National Childhood Vaccine Injury Act of 1986

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INTRODUCTION

Vaccination against infectious illnesses provides unseen protection against contagious diseases—afflictions causing permanent disability or even death. Vaccines have been responsible for dramatic decreases in morbidity and mortality secondary to infectious disease, and in the case of smallpox, has globally eradicated a once life-threatening illness.[1–7] However, while true adverse consequences of vaccination have never exceeded the level of adverse consequences of infection in the absence of vaccination, the public perception of harm secondary to vaccine administration has threatened to overshadow the victory of disease prevention.[1–8] With the inception and continued evolution of immunization, the number of individuals protected against diseases has steadily increased. Unfortunately, the number of vaccine-related adverse events has also increased proportionally to vaccine use.[2]

Historical Advancements

Immunization against infectious disease has saved more lives than any other health intervention in the history of modern medicine.[2,8] The success of continued disease prevention, however, directly correlates to continued immunobiological research, vaccine availability, and those clinicians who administer vaccinations.

Vaccination Against Childhood Diseases: The Controversy

The National Childhood Immunization Program has proven to be one of the most successful health promotion practices in medicine.[8,9] The production of disease-specific vaccines has been lauded as one of the second millennium's greatest accomplishments.[10] In spite of this, however, more than 20% of U.S. two-year-olds remain susceptible to preventable illness by not receiving primary immunizations on schedule.[11,12] This is due in part to socioeconomic and health care accessibility barriers, but also to a loss of parental confidence in immunization programs. Religious or philosophical exemptions account for roughly 0.58% of U.S. children who do not receive immunizations.[13] The risk-to-benefit issue has been argued since the introduction of smallpox vaccine and remains a subject of contention for some. In 1904, in the case *Jacobson v. Massachusetts*, the U.S. Supreme Court ruled in favor of routine smallpox innoculation despite "quite often" serious, and sometimes, fatal side effects.[1] The basis for this ruling was predicated upon the idea that overall societal good outweighs individual rights when prevention of contagious disease is at stake.

Vaccine Adverse Events

Untoward vaccine effects are variable, manifesting from injection site irritation, fever, and irritability to encephalopathy, paralysis, and even death.[14–23] Reporting of certain vaccine adverse events to the Vaccine Adverse Event Reporting System (VAERS) is mandatory. VAERS was established by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) to facilitate the process of gathering postmarketing surveillance data on vaccine-related adverse events.[2] VAERS reports record adverse events temporally but not necessarily causally associated with vaccination.[24]

Manufacturer Liability

Adverse events secondary to vaccine products have inspired lawsuits against vaccine manufacturers.[1] Two theories of tort (duties created by law regarding professional conduct) are reviewed when litigation against a vaccine manufacturer ensues. The first regards safe vaccine development, with a vaccine manufacturer strictly liable for defective vaccine products. Liability cases involving defective vaccines rarely occur, and manufac-

turers are not held liable for inherent or unavoidable adverse events under the theory of strict liability. Second, a manufacturer is responsible for providing adequate warning of possible side effects. Prior to 1986, a manufacturer had to prove that despite adequate warning, the plaintiff would still have received the necessary innoculation.[1]

THE VACCINE INJURY ACT OF 1986

Escalating numbers of lawsuits, primarily aimed at DTP vaccine manufacturers during the 1970s and 1980s, forced many manufacturers from the market. The remaining manufacturers increased DTP vaccine prices, making the limited products available very expensive.[2,5] Widespread vaccine shortages combined with exorbitant increases in vaccine costs placed mandatory vaccination protocols for school-aged children in serious threat of discontinuation. A battle fought largely by the American Academy of Pediatrics called for government reform to ensure the future of the U.S. vaccine supply and continuation of mass immunization programs.[8] In 1986, Congress passed the National Childhood Vaccine Injury Act (NCVIA), administered by the Department of Health and Human Services. This legislation was aimed at the "prevention of human infectious disease through immunization and to achieve optimal protection against adverse reactions to vaccines."[25] The NCVIA program responsibilities include continuation of vaccine research and development, licensing, distribution, and monitoring.[26]

The NCVIA is a no-fault, nontort compensation program for persons injured by certain covered vaccines. The purpose of a no-fault compensation program is to resolve the controversy surrounding government-mandated administration of vaccines for school-aged-children.[27] The NCVIA applies to any vaccine containing diphtheria, tetanus, pertussis, measles, mumps, rubella, poliovirus, hepatitis B, *H. influenzae* type b, and varicella or conjugate pneumococcal antigens.[28] With the probability that rare instances of injury will ensue during mass innoculation practices, the act provides insurance coverage against adverse vaccine events.[4]

The National Vaccine Injury Compensation Program

To effectively address the vaccine litigation crisis, the Vaccine Injury Compensation Program (VICP) was established by the NCVIA and became effective on October 1, 1988.[29] The directive of the VICP is to bring together information about vaccinations (VAERS was officially adopted in 1990), collaborate with the CDC for developing vaccine administration information forms, promote the development of safer vaccines, and establish a federal compensation program for those injured by covered vaccines. The compensation program is funded via an excise tax on vaccines compensable under the

Table 1 Vaccine Injury Table (effective date: December 18, 1999)

Vaccine	Adverse event and time period for manifestation
Tetanus toxoid	Anaphylaxis within 4 hours; brachial neuritis within 2–28 days
Whole-cell pertussis bacteria, partial cell pertussis bacteria, specific pertussis antigens	Anaphylaxis or anaphylactic shock within 4 hours; encephalopathy or encephalitis within 72 hours
Measles, mumps, or rubella virus	Anaphylaxis or anaphylactic shock within 4 hours; encephalopathy or encephalitis within 5–15 days (not less than 5 days, not more than 15 days)
Rubella virus	Chronic arthritis within 7–42 days
Measles virus	Thrombocytic purpura within 7–30 days; vaccine-strain measles viral infection in an immunodeficient recipient within 6 months
Live poliovirus (OPV)	Paralytic polio or vaccine strain polio viral infection within 30 days in an immunocompetent recipient or within 60 days in an immunodeficient recipient.
Inactivated poliovirus (IPV)	Anaphylaxis or anaphylactic shock within 4 hours
Unconjugated Hib vaccine	Early onset Hib disease within 7 days
Conjugated Hib vaccine	No condition specified
Varicella	No condition specified
Pneumococcal conjugate vaccines	No condition specified

(Adapted from Ref. [31,32].)

VICP.[4,30] The VICP largely replaces traditional tort law for deciding vaccine-related injuries and was designed to stabilize the vaccine market by decreasing liability costs of manufacturers and health care providers and to ease reward recovery by eligible claimants.[4,29]

The Vaccine Injury Table

The VICP established the Vaccine Injury Table (VIT) (Table 1) to facilitate the process of justifying compensation to injured vaccinees. The VIT lists specific vaccines with corresponding injuries to be compensated if injury manifests within the predetermined time frame. Therefore, the table eliminates the need for determining a causal relationship between vaccine and injury.[4,5,28,31]

PHARMACY-BASED IMMUNIZATION PRACTICE

Since 1971, the National Center for Health Services Research has recognized the clinical role of pharmacy to include immunization.[28] Pharmacists administered more than 100,000 immunizations in 1997 alone, and as of July 1999, 30 U.S. states officially recognized pharmacists as having the authority to vaccinate.[28,33] As defined by the Model Pharmacy Practice Act of the National Association of Boards of Pharmacy, the practice of pharmacy includes services not limited to compounding, dispensing, labeling, interpreting, and evaluating prescriptions, but also the *administration* and distribution of drugs and devices.[33]

Liability

The liability risk surrounding vaccine providers is relatively low.[33] However, pharmacists administering vaccines can be held liable for negligent administration of vaccines and should take precautions to prevent adverse events. Several important duties surround the administration of vaccines. Health care professionals wishing to immunize should have adequate training in vaccine protocols (including proper management of rare anaphylactic reactions) and administration techniques and maintain current CPR certification.[33] Pharmacists requiring up-to-date immunization information should be familiar with the Web site www.immunofacts.com for vaccine-related information and current standards of practice. Pharmacists must also thoroughly review indications and contraindications to vaccine use and provide adequate consent information defining possible untoward events. Failure to warn represents the bulk of litigation suits. Thus, pharmacists should be aware of vaccine contraindications and keep abreast of information regarding possible adverse outcomes.[1]

Protection Under the NCVIA

Clinicians administering vaccines covered by the NCVIA are protected against litigation surrounding possible vaccine-related adverse events.[33] Pharmacists are commonly involved with the administration of pneumococcal 23-valent and influenza virus vaccines—vaccines not currently covered by the NCVIA.[28] Despite this, pharmacists should be familiar with this far-reaching legislation and understand both the ramifications and limitations on vaccine coverage.

Required Documentation

Health care practitioners administering vaccines covered by the NCVIA are required to record pertinent information in either a permanent patient record or a vaccine log. The patient's name, date of administration, vaccine name, manufacturer, lot number, provider name, address, and title are all required.[33–35] Administration of a NCVIA-covered vaccine also requires practitioners to give vaccine information statements (provided by state health departments and the CDC at www.cdc.gov/nip/publications/VIS/default.htm) to patients or guardians outlining product use, benefits, risks, and warnings.[33,34,36,37] Pharmacists involved with the administration of pneumococcal, influenza, and other vaccines should also adopt this practice.

Mandatory Reporting

In the event of an adverse vaccine event, it is the practitioner's responsibility to contact the VICP for information on how to file a claim, eligibility, and required documentation. Also, the NCVIA mandates reporting to the VAERS for any adverse event covered by the VICP, some of which are specifically listed in the vaccine injury table.[2,34,38]

SUMMARY

Society has a vested interest in routine immunization practices.[2,39] Although many vaccine-preventable dis-

eases are controlled and even eliminated in some regions of the world, complete eradication (with the exception of polio) is unlikely in the near future.[2] Although the conred benefit received from mass immunization is among the greatest of public health achievements, the fact remains that vaccine products are not completely safe. Under the NCVIA, research and development of new vaccine products will also foster the production of safer and more efficacious vaccines. Further attributes of the NCVIA include the VICP along with VAERS and their capability for accumulating data regarding the safety of vaccines.

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PROFESSIONAL ORGANIZATIONS

National Committee for Quality Assurance

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INTRODUCTION

Since the early 1980s, there has been a more than fivefold increase in the number of Americans enrolled in HMOs, which has had a dramatic impact on the delivery of healthcare in the United States. As a result of this trend, HMOs realized the need to demonstrate the quality of care they provided to their members compared with fee-for-service health plans; however, at the time the industry lacked established standards. Subsequently, various independent review processes evolved, which often did not have consistent assumptions about the parameters that defined quality. It was not until the late 1980s that a group of HMO industry leaders recognized that an organization called the National Committee for Quality Assurance (NCQA) had the potential to act as an independent authority on quality control in managed care.[1]

The NCQA is a private, not-for-profit organization that was originally founded in 1979 by two managed care trade associations; however, for 8 years, the organization remained relatively inactive.[1–3] In 1988, a series of meetings were held with the benefits managers of Fortune 500 companies that had experience in external quality assessment, and the evolution of the NCQA was mandated. With a grant from the Robert Wood Johnson Foundation and financial support from the managed care industry, funding was provided for the development of the NCQA, and in the spring of 1990, the NCQA was officially launched.[1,4]

The primary activities of the NCQA are assessing and reporting on the quality of the managed health care plans; the mission is to provide information that enables purchasers and consumers of managed health care to distinguish among plans based on quality, thereby allowing them to make more informed healthcare purchasing decisions.[5] The primary method by which the NCQA evaluates managed care health plans (i.e., managed care organizations, managed behavioral healthcare organizations, preferred provider organizations) involves accreditation and reporting on Health Plan Employer Data and Information Set (HEDIS) measures.[2] The NCQA also has developed or participated in other benchmark programs, including the Consumer Assessment of Health Plans Study (CAHPS, a comprehensive survey of health plan member satisfaction developed by the Agency for Healthcare Quality and Research) and accreditation/certification programs.[2]

NCQA ACCREDITATION SURVEY

The accreditation process for managed care organizations is strictly voluntary, and before accreditation can be pursued, several criteria must be met. The care provided must include adult and pediatric medical/surgical services, obstetrics, mental health care, and preventive care. Furthermore, the plan must provide ambulatory and inpatient services, have been in operation for 2 or more years, have a review process in place to continually improve care, and have access to patients' clinical records.[2] The accreditation survey consists of on- and off-site components, which are conducted by a team that typically consists of physicians and experts in managed care. More than 60 different standards are used to evaluate the clinical and administrative systems of the health plan during the accreditation survey (Table 1).[2] In particular, the survey is used to evaluate the efforts of health plans to continuously improve the quality of care provided and the service it delivers. The findings of the survey teams are reported to a national oversight committee of physicians that assigns one of five possible accreditation levels (excellent, commendable, accredited, provisional, denied). Other accreditation categories include appealed by plan, in process, revoked, scheduled, suspended, and under review by NCQA. The NCQA views accreditation as an ongoing learning process; therefore, it does not assign pass or fail grades. Instead, the accreditation process offers health plans an opportunity to identify how they can improve their services. Initially, only the NCQA and the health plan had access to the accreditation results; now the accreditation status of most health plans can be accessed via the Internet.[2] Historically, HMOs are the principal groups that have pursued accreditation; however, more recently, the NCQA launched a preferred provider organization accreditation program.[2]

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006213

Table 1 Classification of accreditation survey standards

Category	Example
Access and service	Do health plan members have access to the care and service they need? • Are providers in the health plan free to discuss all available treatment options? • Do patients report problems getting the necessary care? • How well does the health plan follow up on grievances?
Qualified providers	Does the health plan assess each provider's qualifications and what health plan members say about their providers? • Does the health plan regularly check the licenses and training of providers? • How do health plan members rate their personal doctor or nurse?
Staying healthy	Does the health plan help people maintain good health and avoid illness? • Does it give its doctors guidelines about how to provide appropriate preventive health services? • Are members receiving tests and screenings as appropriate?
Getting better	How well does the health plan care for people when they become sick? • How does the health plan evaluate new medical procedures, drugs, and devices to ensure that patients have access to safe and effective health care?
Living with illness	How well does the health plan care for people with chronic conditions? • Does the plan have programs in place to assist patients in managing chronic conditions such as asthma? • Do diabetics, who are at risk for blindness, receive eye exams as needed?

(From Ref. [2].)

HEDIS

Another means by which the NCQA evaluates health plans is via HEDIS reporting, which differs from the accreditation process in that HEDIS measures the performance and not the quality of systems or processes in the health plan. The primary objective of HEDIS reporting is to provide purchasers of health plan services (i.e., employers) with objective information about the relative value and accountability of health plans by focusing on basic areas of performance (Table 2).[6] Essential services evaluated with HEDIS include preventive medicine (e.g., immunization and screening programs), prenatal care, acute and chronic disease management, and mental health programs. Other areas of performance that are included in HEDIS measures include member access and satisfaction, health plan utilization, and financial stability of the health plan.[6] The Committee on Performance Measurement identifies areas of priority for which measures should be developed.[2] The responsibility of developing the actual measure is left up to the Measurement Advisory Panels, which identify the best measures and methodologies for assessing healthcare performance. Via the Measurement Advisory Panels, measures are updated on a regular basis to reflect advancements in performance measurement and information systems technology, as well as changes in the managed care industry.

ACCREDITATION AND CERTIFICATION PROGRAMS

Beginning in 2002, the NCQA will implement a flexible health plan evaluation program that applies to various

Table 2 Examples of effectiveness of care measures in HEDIS 2000

Childhood/adolescent immunization status	Breast cancer screening
Chlamydia screening in women	Cervical cancer screening
Prenatal care in first trimester/check-ups after delivery	Controlling high blood pressure
Cholesterol management after heart attack	Comprehensive diabetes care
Use of appropriate medications for people with asthma	Beta blocker treatment after a heart attack
Follow-up after hospitalization for mental illness	Antidepressant medication management
Advising smokers to quit	Flu shots for older adults
Medicare health outcomes survey	

(From Ref. [6].)

services provided by healthcare organizations.[7] Examples include the following:

- Healthcare organizations that offer disease-management services to patients or providers can apply for disease-management accreditation (health plans that provide comprehensive services) or certification (organizations that provide clinical systems to support disease management).
- Physician groups or organizations can apply for NCQA certification, which is similar to the managed care accreditation process and allows the physician groups to demonstrate the quality of their healthcare services.
- Healthcare organizations or physician groups/organizations that are not eligible for managed care accreditation programs can apply for certification in utilization management and credentialing, which allows them to demonstrate the quality of their healthcare services in a manner consistent with managed care organizations.
- Organizations or departments that verify the credentials of healthcare providers can apply for NCQA certification.

NCQA QUALITY COMPASS AND THE STATE OF MANAGED CARE QUALITY REPORT

The NCQA Quality Compass is a compilation of accreditation and HEDIS information from hundreds of health plans. Contained in this document are national and regional averages and benchmarks, which can be used to identify areas for improvement in a particular health plan. Based on the information compiled in the Quality Compass, the NCQA produces an annual State of Managed Care Quality Report, which is a broad assessment of the overall performance of managed care throughout the United States. Similar to the Quality Compass, the Report includes national and regional averages for key performance measures and identifies the levels of performance that are attainable. The Report also uses the information to extrapolate the benefits on the nation's health if all health plans performed at the benchmark level.[2]

Table 3 2000 NCQA Board of Directors

Barbara A. Brickmeier (IBM Global Benefits)
Mark Chassin, MD (Mt. Sinai Medical Center)
James Cubbin (General Motors Corporation)
Robert S. Galvin, MD (General Electric Company)
Charles M. Gayney (UAW Social Security Department)
Alice G. Gosfield, Esq. (Alice G. Gosfield & Associates, PC)
Alan Hoops (PacifiCare Health Systems)
David Kessler, MD, JD (Yale School of Medicine)
Trudy Lieberman (Consumer Reports)
John M. Ludden, MD (Harvard Medical School)
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Ira Millstein, JD (Weil, Gotshal & Manges)
Margaret E. O'Kane (NCQA)
Thomas R. Reardon, MD (American Medical Association)
Neil Schlackman, MD (Aetna, US Healthcare)
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Table 4 NCQA contact information

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Web site: http://www.ncqa.org

NCQA/HEDIS AND PHARMACY PRACTICE

Pharmacy performance measures have been included in the managed care health plan accreditation process as well as in HEDIS. Therefore, pharmacists can play an important role in the process by understanding and utilizing the NCQA/HEDIS indicators and performance measures as a guide to improving patient care.[8] Pharmacists also play an important role in the accreditation/certification process of other healthcare organizations by providing input and participating in disease-management services as well as utilization management.

NCQA INFORMATION

Members of the 2000 NCQA Board of Directors are listed in Table 3. NCQA contact information is shown in Table 4.

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National Community Pharmacists Association

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INTRODUCTION

The National Community Pharmacists Association (NCPA) was established on October 20, 1898 in St. Louis, Missouri, as the National Association of Retail Druggists (NARD), a name it held until 1996. The organization was conceived by a small group of independent community drugstore owners from major metropolitan areas in the East and Midwest, who chose to band together for the express purpose of protecting their professional practice and economic livelihood from a stamp tax on proprietary medicines to fund the Spanish-American war. From this modest organizational effort (predictably over a legislative matter) to coalesce a national group representing both the professional and proprietary interests of independent retail pharmacy grew one of the most powerful national associations—pharmacy or otherwise—ever to grace the halls of Congress. In 1937, in the wake of two extraordinary congressional victories that ensured the enactment of the landmark Robinson–Patman Anti-Discrimination Act and the Tydings–Miller Fair Trade Law—both of which remain foundations of protections for small business— *Business Week* Magazine labeled NARD "the most powerful trade association today."

HISTORICAL OVERVIEW

Due to its tenacity, singularity of purpose (promoting the cause of the independent community pharmacist), and the grassroots strength of its active and vocal membership, NARD/NCPA earned the respect of its adversaries as well as of its allies, including several U.S. presidents. The issues confronting independent pharmacists at the turn of the 20th century have a familiar ring to today's practitioners—price cutting, price protection, price discrimination, fair trade, mail order, physician dispensing, and encroachments by the federal government on the practice of the pharmacy profession. Legislative accomplishments of NARD/NCPA during the latter half of the 20th century sought to address these issues, particularly as they relate to discriminatory pharmaceutical pricing and other practices (such as the Prescription Drug Marketing Act of 1988, designed to stop illegal prescription drug diversion, and "best price" legislation in 1990 requiring manufacturers to offer their best prices in the Medicaid drug program); retaining consumers' "freedom of choice" to patronize the pharmacy of their choice through enactment of state laws inspired by NARD/NCPA model legislation; preserving practices traditionally reserved for the pharmacy profession (such as compounding); and allowing pharmacists to collectively negotiate third-party contracts (in the 106th Congress as the Quality Health Care Coalition Act).

Concurrent with these legislative concerns, NARD/NCPA also provided leadership in advancing professional issues affecting its membership and the public it serves. Examples of this leadership included NARD/NCPA-supported "Ask Your Pharmacist" labeling on over-the-counter medicines, a 20-year campaign that culminated in 1999 with a Food and Drug Administration (FDA) directive permitting such labeling; the creation of the National Institute for Pharmacist Care Outcomes (NIPCO), an organization devoted to advancing pharmacist care services through a disease management certification program for pharmacists; and coalition-building to create the National Institute for Standards in Pharmacist Credentialing, a national model and process for credentialing pharmacists in disease state management.

NCPA is entering its 103rd year as the sole organization representing the interests of independent community pharmacists. New challenges for the organization and its members lie ahead in the new millennium—surviving in a managed care environment, fine-tuning

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DOI: 10.1081/E-ECP 120006212

pharmaceutical delivery services to ensure fair compensation, enhancing professional knowledge through credentialing to deliver the highest levels of personalized pharmacist care, and continuing to refine the mission of the profession.

ORGANIZATIONAL STRUCTURE AND GOVERNANCE

The current organizational and governance structure of NCPA is essentially unchanged from that created by the organization's founding fathers in 1898, and has served as its enduring strength in the intervening 102 years. The structure consists of a full-time salaried Executive Vice-President, who serves as the Chief Executive Officer of the Association, as well as eight officers and six members of the Executive Committee, elected to staggered terms of office once a year. The officers and members of the Executive Committee (OEC), which also includes the Executive Vice-President as an ex-officio member, are responsible for the management of association priorities and activities.

The OEC are named at the annual meeting of the association's House of Delegates, which meets once a year at NCPA's Annual Convention. Officers and Executive Committee members typically serve a period of 12 to 14 years in association leadership as each moves up the ladder of responsibility (for example, from fifth Vice-President to fourth Vice-President, service on the Executive Committee, President-Elect to President).

The House of Delegates is comprised of representatives, who are appointed by their respective state or local pharmacy associations, to serve in this policy-making body. The House of Delegates provides policy guidance to the association's OEC through deliberations and passage of resolutions and policy positions, which are generated by eight standing committees that meet each year to formulate policy directives.

The eight committees are consumer affairs and public relations, home healthcare pharmacy services, long-term care pharmacy services, independent pharmacy chains, management, national legislation and government affairs, third-party payment programs, and professional relations. One NCPA member from each state is nominated by his or her state or local pharmacy association and appointed by the NCPA president to serve on a committee. The committees review and evaluate current NCPA policies and activities, develop recommendations for existing and new projects, and offer suggestions on how best to respond to the emerging needs and challenges of the pharmacy marketplace.

The House of Delegates and standing committees structure ensures that the NCPA membership at large has the opportunity to provide maximum input into association policies and programs.

The leadership of the NCPA can be found at ncpanet.org.

Executive Vice President:
Calvin J. Anthony, P.D.

MISSION

The mission of the association is quoted as follows:

- We are dedicated to the continuing growth and prosperity of independent community pharmacy in the United States.
- We are the national pharmacy association representing the professional and proprietary interests of independent community pharmacists and will vigorously promote and defend those interests.
- We are committed to high-quality pharmacist care and to restoring, maintaining, and promoting the health and well-being of the public we serve.
- We believe in the inherent virtues of the American free enterprise system and will do all we can to ensure the ability of independent community pharmacists to compete in a free and fair marketplace.
- We value the right to petition the appropriate legislative and regulatory bodies to serve the needs of those we represent.
- We will utilize our resources to achieve these ends in an ethical and socially responsible manner.

CURRENT MAJOR INITIATIVES OR DIRECTIONS

The year 1999–2000 ushered in the second century of independent pharmacy service to the nation's communities and NCPA's existence as the only national association representing independent pharmacy. The new millennium finds the association's membership robust and thriving, thus stemming a decade-long decline in independent store count brought about by a difficult managed care envi-

ronment and aggressive chain drugstore and mail order incursions in the marketplace.

There are nearly 25,000 single-store independent pharmacies, independent chains, independent franchises, and independent pharmacist-owned supermarket pharmacies in the United States or nearly half of the 52,600 total stores in the pharmacy sector. Independent pharmacy today represents a $49 billion marketplace, where independents' prescription sales are $41 billion or nearly one-half of the retail prescription market. Independent pharmacies dispense 1.1 billion prescriptions annually.

The average independent's pharmacy sales are $1.97 million, up 37% in the last 3 years; average prescription sales are $1.64 million, up 43% in the last 3 years.

Independents are rated the best pharmacies in America by consumers because of their personal attention, the speed and efficiency of dispensing, and the medication information provided. According to the *1999 Ortho Biotech Retail Pharmacy Digest*, consumers using independent pharmacies reported the highest level of satisfaction, and customers of independent pharmacies were the most likely to recommend their pharmacy to a friend or relative.

Independents are leaders in providing pharmacist care services: Nearly 42% of independents are certified to provide disease management services, and more than 12,000 community pharmacists have completed disease management programs offered by NCPA's National Institute for Pharmacist Care Outcomes (NIPCO).

Highlights of NCPA's 1999–2000 year were forged on both the legislative and technology fronts as the association grappled with the age-old challenges of third-party issues and saw many of its initiatives in the great healthcare reform debate of the early 1990s become standard fare for public embrace. At the same time, NCPA defined a brand new frontier for independents in the realm of the Internet and the World Wide Web.

It was no small achievement that NCPA marshaled widespread support in the House of Representatives for the Campbell/Conyers Bill (the Quality Health Care Coalition Act), calling for collective negotiations by pharmacists and other healthcare providers, free of the shadow of antitrust. By the time of a key vote on the measure, more than one-half of the House of Representatives (220 members), showing broad bipartisan support, signed on as cosponsors of the bill—a clear signal that this was an issue whose time had come. The bill passed the House in late June 2000 by a resounding vote of 276 to 136—a 2 to 1 margin.

Another bill that garnered widespread bipartisan support was the patient bill of rights, which riveted national attention on remedies proposed to improve the quality of health care and eliminate managed care abuses. Chief among the bill's provisions is the restoration of patient rights to have better access to the provider of their choice and prescriptions selected by their physicians.

Another legislative victory for independents was resounding support in both the House and Senate for landmark legislation that enables pharmacists, wholesalers, pharmacy buying groups, independent chains, and other licensed distributors to purchase Food and Drug Administration (FDA)-approved medicines from other countries, including Canada, the United Kingdom, and the European Union. Current law restricts imports to drug manufacturers. The Senate's 74 to 21 vote in July 2000 placed the import legislation before a House–Senate conference committee, where a vote was imminent in late-September.

On the regulatory front, a 20-year campaign waged by NCPA for federal recognition of community pharmacists as vital sources of medication information for consumers earned Food and Drug Administration (FDA) sanction in spring 1999. Pharmacists will now be included on the labeling for over-the-counter (OTC) medications—as in "Ask your doctor or pharmacist." NCPA was prominently featured at the White House ceremony announcing the FDA OTC label recognition.

On the professional development front, the NCPA-created NIPCO continued to lead the way in developing programs that help establish pharmacist care services in community pharmacies. To date, more than 12,000 community pharmacists have completed NIPCO-accredited disease management programs in pharmacist care skills, cardiovascular care, respiratory care, diabetes care, immunization skills, osteoporosis, and mental health.

On the business development front, NCPA and the Chain Drug Marketing Association (CDMA) announced an alliance, which bore fruit as a combined Expo 2000 midyear meeting sponsorship and the promise of other joint marketing programs. CDMA represents more than 100 small and regional drugstore chains.

NCPA was instrumental in the formation and funding of two major foundations that will benefit community pharmacy in 1999. The first is the Institute for the Advancement of Community Pharmacy, which received a $27.5 million grant from Knoll Pharmaceutical Company to benefit community pharmacy. The board of directors is composed of the CEOs of NCPA and the National Association of Chain Drug Stores (NACDS). The second is the result of the distribution of funds from a $723 million

settlement approved by a U.S. district court judge of a price-fixing case involving 20 major brand name pharmaceutical manufacturers. Approximately $18.5 million of settlement proceeds has been set aside for a new foundation, "the Foundation for the Advancement of Retail Pharmacy."

The Internet and World Wide Web became a reality for many of NCPA's members. In August 1999, CornerDrugstore.com was launched as the first national Internet solution for independents. Community pharmacists signed up in droves to become part of the largest virtual network of independents anywhere in the nation. Independents could build their own web sites by using CornerDrugstore.com templates, or join their web site in the national network hosted by CornerDrugstore.com. To date, more than 4000 independent pharmacies have enrolled in the program, which has earned the endorsement of more than 50 pharmacy organizations.

Lastly, NCPA and TheraCom, Inc., a leading provider of specialty drugs, formed the Specialty Drugs Network in early 2000. The Specialty Drugs Network represents the largest and most comprehensive network in the United States for the distribution, administration, and care of patients in need of specialty drugs. The network will enable independent pharmacists to dispense a growing array of specialty pharmaceuticals for those drugs they choose to dispense and with "just-in-time" inventory control that offers cost-effective management of these medications. The network also offers professional education to build clinical competency through a specialty pharmaceuticals certificate training program.

In all, 1999–2000 was a good start to the second century—the new millennium—for the independent. As the figures indicate, independent community pharmacy has become a formidable market force, one to be reckoned with in the years ahead.

National Institute for Standards in Pharmacist Credentialing

Walter J. Morrison
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INTRODUCTION

The National Institute for Standards in Pharmacist Credentialing (NISPC) was formed in 1998 by the American Pharmaceutical Association, the National Association of Boards of Pharmacy (NABP), the National Association of Chain Drug Stores, and the National Community Pharmacists Association. These organizations developed NISPC to satisfy the need for a nationally recognized credentialing process that establishes appropriate national standards of care for, and facilitates recognition of the value of, disease state management (DSM) services provided by pharmacists.

As the scope of pharmacy practice continues to expand to meet the needs of a more health-conscious, knowledgeable consumer and the cost-containment concerns of managed care organizations, pharmacists are working with patients, physicians, and other providers to provide disease-specific primary care services. NISPC-credentialed pharmacists have demonstrated via a national examination process that they possess the competencies required to provide disease-specific services that merit inclusion in public and private health plans. Consequently, the NISPC credential facilitates prudent managed care plan design and payment decisions. Because of the focus on cognitive services for which payment can be expected, the NISPC credential also can be expected to facilitate the transition from practices which are primarily distributive to those that have a better balance between distributive and cognitive services. The NISPC credentialing process provides the most viable approach to achieve the acceptance of pharmaceutical care in the national marketplace.

Pharmacists are providing DSM services to help patients manage such chronic diseases as asthma, diabetes, and dyslipidemia, and drug therapies such as anticoagulation. Hundreds of pharmacists, including those serving on college faculties, have made the decision to seek NISPC credentialing. They agree that the NISPC credential provides the national recognition and assurance that patients and payers will require of pharmacists who choose to provide disease-specific patient management services.

ORGANIZATIONAL STRUCTURE/MEETINGS

NISPC is an autonomous and independent agency with a four-member Board of Directors, one from each of the founding organizations, and an Executive Director. In April 2000, Dr. Walter J. Morrison was selected to serve as the first Executive Director by the NISPC Board of Directors. The NISPC board includes Calvin J. Anthony, Executive Vice President, National Community Pharmacists Association; Carmen A. Catizone, Executive Director/Secretary, National Association of Boards of Pharmacy; John A. Gans, Executive Vice President/CEO, American Pharmaceutical Association; and Kurt A. Proctor, Senior Vice President, National Association of Chain Drug Stores. Mr. Anthony has served as president since incorporation. The NISPC Board of Directors has scheduled quarterly meetings, usually on the day immediately preceding the quarterly meetings of the Joint Commission of Pharmacy Practitioners (JCPP).

To provide assurance that the competencies, standards, and objectives on which the respective examinations are based remain current, NISPC has established a Standards Review Board. A Payers Advisory Panel has been established to provide recommendations related to the ambulatory care credentialing needs of firms paying for those primary health care services provided by pharmacists. NISPC is advised by a Standards Review Board and Payers Advisory Panel, which provide a broad coalition of

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DOI: 10.1081/E-ECP 120006295

professional and industry representation, including boards of pharmacy, colleges of pharmacy, interdisciplinary health professionals, national health care associations, payers, pharmaceutical manufacturers, practitioners, public/consumer advocates, quality assessment organizations, and state pharmacy associations. These advisory groups are scheduled to meet annually.

NISPC DSM EXAMINATIONS

Under an agreement with NISPC, the NABP has developed examinations that are psychometrically valid and legally defensible. NISPC currently offers four disease-specific examinations that assess a pharmacist's competency in the management of diabetes, dyslipidemia, asthma, and anticoagulation therapy. Pharmacists can pursue credentialing in one, two, three, or all four areas of practice. NISPC DSM examinations are administered daily in a computer-based format through LaserGrade, Inc.'s, nationwide system of testing centers. Each exam consists of multiple-choice questions and takes approximately 3 hours to complete. Results are made available in 7 to 10 business days.

Pharmacists who earn a passing score on the NISPC DSM examinations are credentialed and issued a certificate by NISPC. The certificate documents to employers, peers, and the public that they possess the knowledge and skills to provide disease-specific services to patients. NISPC-credentialed pharmacists are recognized on the NISPC and NABP web sites.

Information about the NISPC DSM examinations is available in the *Disease State Management (DSM) Examination Registration Bulletin.* In addition to a registration form and information about the testing procedures, the *Bulletin* contains the competency statements, or blueprint, upon which the DSM examinations are developed. Also included in the *Bulletin* are the standards and objectives for each DSM examination. Cross-referenced to the competency statements, the standards and objectives delineate the knowledge base expected of pharmacists providing disease-specific primary care services.

Examination Eligibility Requirements

Pharmacists seeking the NISPC credential must be licensed in good standing with their state board of pharmacy to sit for the examinations. The NISPC DSM exams are designed to assess the competencies of practicing pharmacists with 2 or more years of experience; however, there is no traditional practice experience requirement. Demonstrated competence, rather than years of experience, is the factor being evaluated. Also, unless the exams are being used as personal assessment tools, continuing professional education programs designed to prepare pharmacists for NISPC examinations are strongly recommended. During the first 2 years, the exams were offered, 1649 pharmacists took 1973 examinations with a success rate of 56%.

Exam Registration Process

The cost of a single NISPC DSM examination is $135. If a person registers for two or more exams on the same registration form, there is a charge of $135 for the first and $110 for each additional exam. To register for an examination, contact the NISPC Testing Center to request a *DSM Registration Bulletin.* Also available is the electronic testing *DSM Examinations Candidate's Review Guide* (CRG), which contains information about the examinations and sample questions. The CRG may be purchased for $10 through the NISPC Testing Center or downloaded for free from the NISPC web site (www.nispcnet.org). A CRG order form is also included in the *DSM Registration Bulletin.* The NISPC Testing Center address is 700 Busse Highway, Park Ridge, IL 60068. The Center phone number is (847) 698-6227, the fax number is (847) 698-0124, and the e-mail address is dsm@nabp.net.

ACTIVITIES AND ISSUES

NISPC will continue to support efforts to revise state and federal laws and regulations that limit a pharmacist's ability to provide DSM services. State boards of pharmacy will be encouraged to adopt the NISPC competencies, standards, and objectives, and to provide for inspectors that are credentialed and competent to evaluate the quality of care that is being provided. The preceding will position boards to address any complaints brought to their attention regarding the quality of care provided by the pharmacists they have licensed. Colleges of pharmacy will be encouraged to make available the knowledge and skills that will adequately prepare their graduates to pass the NISPC exams immediately after licensure. Colleges and pharmacy associations will be encouraged to provide continuing professional education with the depth and breadth of content required for success on the NISPC exams. They will also be encouraged

to develop implementation manuals and "safety nets" to facilitate decisions regarding the provision of DSM services. NISPC will be encouraging those conducting studies to adopt standardized data collection procedures to address the need for significant studies with documented results.

In addition to the annual critique of the respective competency statements, standards, and objectives, the following outstanding issues will require consideration by the NISPC advisory groups and disposition by the Board of Directors:

- The need for practical and written exams to meet credentialing requirements.
- Recertification requirements.
- Establishment of an appropriate approach for pharmacists to indicate that they have satisfied NISPC credentialing requirements.
- Expansion of the current dyslipidemia exam to cover all coronary vascular-related diseases, except coronary heart failure.
- Consideration of other pharmacist/pharmacy ambulatory care credentialing needs, if recommended by the Payers Advisory Panel.

Walter J. Morrison, the former Executive Director, National Institute Standards in Pharmacist Credentialing prepared this document.

National Institutes of Health

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INTRODUCTION

Founded in 1887, the National Institutes of Health (NIH) is one of the world's foremost biomedical research centers, and the federal focal point for medical research in the United States. The NIH, comprised of 27 separate institutes and centers, is one of eight health agencies of the Public Health Service, which, in turn, is part of the U.S. Department of Health and Human Services[1] (For information on the history of NIH, visit http://www.nih.gov/od/museum/.)

The goal of NIH research is to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability, from the rarest genetic disorder to the common cold. The NIH mission is to uncover new knowledge that will lead to better health for everyone and works toward that mission by conducting research in its own laboratories; supporting the research of nonfederal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helping in the training of research investigators; and fostering communication of medical and health sciences information.

Scientific progress depends mainly on the work of dedicated scientists. About 50,000 principal investigators—working in every state and in several foreign countries, from every specialty in medicine, every medical discipline, and at every major university and medical school—receive NIH extramural funding to explore unknown areas of medical science. Supporting and conducting both NIH's extramural and intramural programs are about 15,600 employees, more than 4000 of whom hold professional or research doctorate degrees. The NIH staff includes intramural scientists, physicians, dentists, veterinarians, nurses, pharmacists, and laboratory, administrative, and support personnel, plus an ever-changing array of research scientists in training.

The rosters of those who have conducted research, or who have received NIH support over the years include the world's most illustrious scientists and physicians. Among them are 97 scientists who have won Nobel Prizes for achievements as diverse as deciphering the genetic code and learning what causes hepatitis. Five Nobelists made their prize-winning discoveries in NIH laboratories: Drs. Christian B. Anfinsen, Julius Axelrod, D. Carleton Gajdusek, Marshall W. Nirenberg, and Martin Rodbell.

CONTRIBUTIONS TO PUBLIC HEALTH

NIH is a key element in a partnership that has thrived for decades and includes universities and academic health centers, independent research institutions, and private industry, where research programs and product development activities help make federally funded research findings more widely available. The partnership, which has produced many of the medical advances that benefit Americans today, also includes voluntary and professional health organizations, and the Congress, which consistently has supported this vast enterprise.

NIH research has played a major role in making possible the following achievements of the last few decades: Mortality from heart disease, the number one killer in the United States, dropped by 36% between 1977 and 1999. Death rates from stroke decreased by 50% during the same period. Improved treatments and detection methods increased the relative five-year survival rate for people with cancer to 60%. Paralysis from spinal cord injury is significantly reduced by rapid treatment with high doses of a corticosteroid. Treatment given within the first 8 h after injury increases the likelihood of recovery in severely injured patients who have lost sensation or mobility below the point of injury. Long-term treatment with anticlotting medicines cuts stroke risk by 80% from atrial fibrillation. In schizophrenia, where patients suffer frightening delusions and hallucinations, new medications can reduce or eliminate these symptoms in 80% of patients. Chances for survival increased for infants with respiratory distress syndrome, an immaturity of the lungs, due to development of a substance to prevent the lungs from collapsing. In general, life expectancy for a baby born today is almost three decades longer than one born at the be-

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006186

ginning of the century. With effective medications and psychotherapy, the 19 million Americans who suffer from depression can now look forward to a better, more productive future. Vaccines protect against infectious diseases that once killed and disabled millions of children and adults. Dental sealants have proved 100% effective in protecting the chewing surfaces of children's molars and premolars, where most cavities occur. In 1990, NIH researchers performed the first trial of gene therapy in humans. Scientists are increasingly able to locate, identify, and describe the functions of many of the genes in the human genome with the ultimate goal of developing screening tools and gene therapies for cancer and many other diseases.

INSTITUTES, CENTERS, AND OFFICES

The NIH is an amalgam of many diverse research and support organizations (Fig. 1). A list of NIH's 27 Institutes and Offices (along with links to their web sites) is available at http://www.nih.gov/icd/. The missions and activities of the Institutes and Centers are described at http://www.nih.gov/icd/programs.htm. The Institutes include the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Mental Health, the National Institute of Allergy and Infectious Diseases, and the Human Genome Research Institute. Centers include the Vaccine Research Center, the Fogarty International Center, the Center for Scientific Review, and the National Center for Complementary and Alternative Medicine. Other notable components of the NIH are the Warren Grant Magnuson Clinical Center, Office of Social and Behavioral Research, and the National Library of Medicine.

Campus and Facilities

NIH intramural scientists conduct their research in laboratories located on a 300-acre campus in Bethesda, and in several field units across the country and abroad. Maps of the campus and of the local area are located at http://www.nih.gov/about/maps.html. The Intramural Research Programs, although representing only a small part of the total NIH budget, are central to the NIH scientific effort. First-rate scientists are key to NIH intramural research. They collaborate with one another regardless of institute affiliation or scientific discipline, and have the intellectual freedom to pursue their research leads in NIH's own laboratories. These explorations range from basic biology, to behavioral research, to studies on the diagnosis and treatment of major diseases. Through clinical research, promising discoveries in the laboratories are translated into new therapies and treatments for patients. The NIH also has facilities in the Rockville, Maryland, area and the NCI Frederick Cancer Research and Development Center (FCRDC) at Fort Detrick in Frederick, Maryland. The National Institute of Environmental Health Sciences, which studies the adverse effects of environmental factors on human health, operates from its main facility in Research Triangle Park (RTP), North Carolina. Other laboratory facilities include the NIH Animal Center in Poolesville, Maryland; the National Institute on Aging's Gerontology Research Center in Baltimore, Maryland; the Division of Intramural Research of the National Institute on Drug Abuse, also in Baltimore; the National Institute of Allergy and Infectious Diseases' Rocky Mountain Laboratories in Hamilton, Montana, and several smaller field stations.

The 14-story Warren Grant Magnuson Clinical Center (http://www.cc.nih.gov) is the NIH's hospital and center for clinical research. Patients come from all over the world to participate in clinical studies here. Each year, the Clinical Center admits about 7000 inpatients. The ambulatory clinical research unit accounts for nearly 68,000 outpatient visits per year. Patients at the NIH participate in clinical trials that span a wide range of diseases and conditions. The Clinical Center also houses the Visitor Information Center, which is NIH's information liaison and host to thousands of visitors each year. Construction began in 1997 for the new Mark O. Hatfield Clinical Research Center. The Hatfield Center will house the research hospital's 250 beds for inpatient and outpatient care, outpatient facilities, and research laboratories. It will connect to the current building, which opened its doors in 1953. The hallmark of the original building is the proximity of the patient care to scientific labs. The new facility will amplify the bench-to-bedside tradition, providing a crucial link from the rapidly moving biomedical findings of the laboratory into the mainstream of medical practices. The Clinical Center Pharmacy Department (http://www.cc.nih.gov/phar) provides extensive clinical and research services and conducts several highly regarded training programs. Pharmacists also contribute directly to the NIH intramural and extramural research programs.

Funding

From a total of about $300 in 1887, the NIH budget has grown to more than $20.3 billion in 2001. The NIH is funded through direct appropriations from the U.S. Congress. Approximately 82% of the investment is made through grants and contracts supporting research and

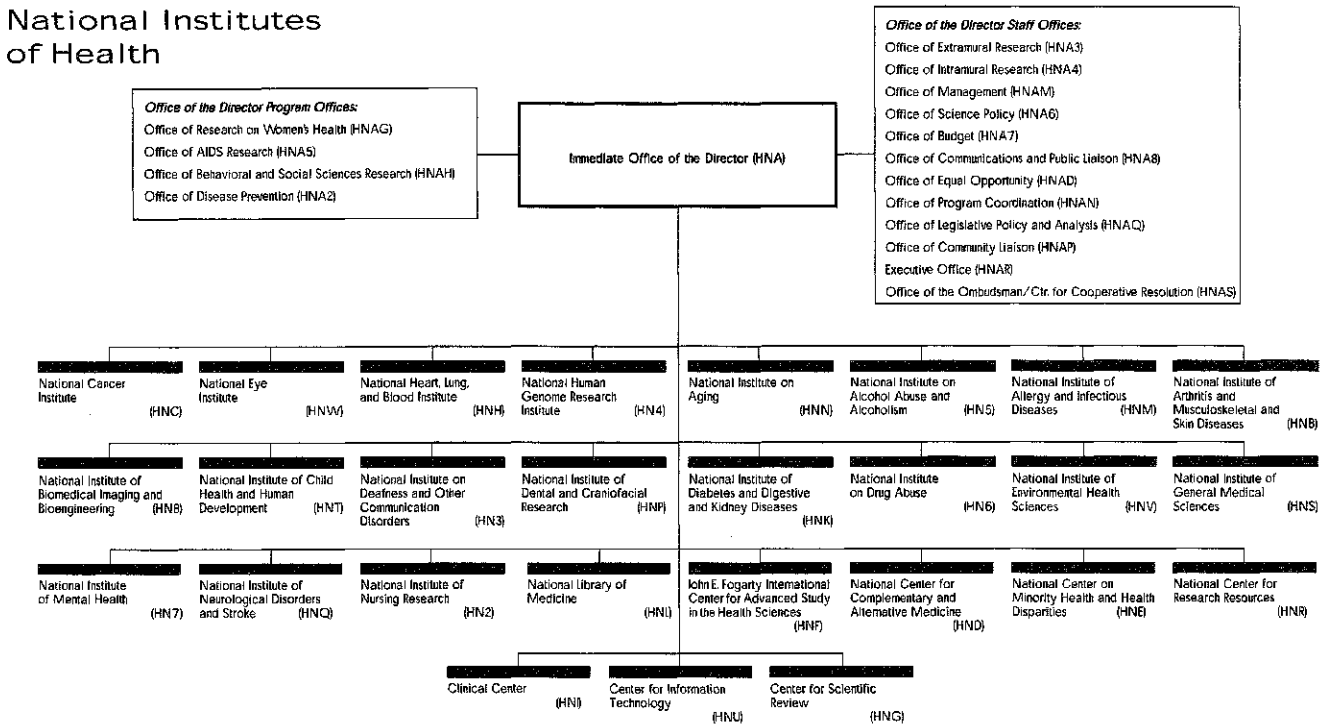

Fig. 1 The Mission of the National Institutes of Health is science in pursuit of knowledge to improve human health. This means pursuing science to expand fundamental knowledge about the nature and behavior of living systems; to apply that knowledge to extend the health of human lives; and to reduce the burdens resulting from disease and disability. The National Institutes of Health seeks to accomplish its mission by: ① Fostering fundamental discoveries, innovative research, and their applications in order to advance the Nation's capacity to protect and improve health; ② Developing, maintaining, and renewing the human and physical resources that are vital to ensure the Nation's capability to prevent disease, improve health, and enhance quality of life; ③ Expanding the knowledge base in biomedical, behavioral, and associated sciences order to enhance America's economic well-being and ensure a continued high return on the public investment in research; and ④ Exemplifying and promoting the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

training in more than 2000 research institutions throughout the United States and abroad. In fact, NIH grantees are located in every state in the country. These grants and contracts comprise the NIH Extramural Research Program. Approximately 10% of the budget goes to NIH's Intramural Research Programs, the more than 2000 projects conducted mainly in its own laboratories. About 8% of the budget is for both intramural and extramural research support costs.

Clinical Studies

Information regarding clinical trials conducted at the NIH Clinical Center in Bethesda, Maryland, can be found at http://clinicalstudies.info.nih.gov/. ClinicalTrials.gov (http://clinicaltrials.gov) provides information on federal and private medical studies at thousands of locations nationwide. Information regarding the types and conduct of clinical trials is also provided.

Training

Clinical research training is an integral part of the NIH mission. Training opportunities are available for students, physicians, other health care professionals, and postdoctoral researchers. These training programs vary in scope and can range from several weeks to several years in duration. Information regarding NIH research training opportunities is available at http://www.training.nih.gov. Several remote-access resources have been developed for training researchers and clinicians. For example, the course on Clinical Research Training (http://www.cc.nih.gov/ccc/cr/index.html) was developed to assist those with an interest in conducting clinical research. Other train-

ing programs are described at http://www.cc.nih.gov/profscientists.cgi.

GRANTS AND CONTRACTS

Information regarding NIH grants and funding opportunities may be found at http://www.grants.nih.gov/grants/index.cfm. The grants page provides information about NIH grant and fellowship programs, policy changes, administrative responsibilities of awardees, the Computer Retrieval of Information on Scientific Projects (CRISP) database, and the numbers and characteristics of awards made by the NIH. CRISP is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions. The database, maintained by the Office of Extramural Research at the National Institutes of Health, includes projects funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Health Care Policy Research (AHCPR), and Office of Assistant Secretary of Health (OASH). Users, including the public, can access the CRISP interface to search for scientific concepts and emerging trends and techniques or to identify specific projects and/or investigators. This grants page also contains information regarding research contracts and research training opportunities and provides access to the NIH Guide for Grants and Contracts. The Guide is the official document for announcing availability of NIH funds for biomedical and behavioral research and research training.

Extramural Research

Final decisions about funding extramural research are made by senior scientific staff at the NIH headquarters. But long before this happens, the process begins with an idea that an individual scientist describes in a written application for a research grant. The project might be small, or it might involve millions of dollars. The project might become useful immediately as a diagnostic test or new treatment, or it might involve studies of basic biological processes with practical value that may not be apparent for many years. Each research grant application undergoes a peer review process. A panel of scientific experts, primarily from outside the government, who are active and productive researchers in the biomedical sciences, first evaluates the scientific merit of the application. Then, a national advisory council or board, comprised of eminent scientists as well as public members who are interested in health issues or the biomedical sciences, determines the project's overall merit and priority in advancing the research agenda of the particular NIH funding institute. Altogether, about 38,500 research and training applications are reviewed annually through the NIH peer review system. At any given time, the NIH supports 35,000 grants in universities, medical schools, and other research training institutions both nationally and internationally.

SCIENTIFIC RESOURCES

Scientific resources available from the NIH are described at http://www.nih.gov/science/. These include research sourcebooks, documents relating to molecular biology and molecular modeling, research labs on the Web, library and literature resources, model organisms for biomedical research, reagent programs, data banks, animal care and use guidelines, NIH-supported human specimen resources, bioethics resources, and lab safety and waste management resources, to name a few. Protomechanics, a guide for intramural scientists on preparing and conducting a research study, is available at http://www.cc.nih.gov/ccc/protomechanics/.

The National Library of Medicine is another principal unit of the NIH. The 10-story Lister Hill Center houses the Lister Hill National Center for Biomedical Communications and the National Center for Biotechnology Information. Both are components of the National Library of Medicine. The Library produces and publishes Index Medicus, a comprehensive monthly listing of articles appearing in the world's leading medical journals. The Library also operates a computerized Index Medicus, known as MEDLINE (PubMed), and has pioneered the introduction of large medical bibliographic databases.

NIH Image is a public domain image processing and analysis program for the Macintosh. It was developed at the Research Services Branch (RSB) of the National Institute of Mental Health (NIMH), part of the National Institutes of Health (NIH). The software is located at http://rsb.info.nih.gov/nih-image/Default.html.

HEALTH INFORMATION RESOURCES

A wide array of health information is provided by the NIH to consumers and healthcare professionals. The NIH Health Information Index, available at http://www.nih.gov/health/InformationIndex/HealthIndex/Pubincov.htm, provides information on diseases currently under investigation by NIH or NIH-supported scientists and

major NIH research areas with links to the appropriate institute(s), center(s), or other component(s) to call for information, along with the appropriate phone numbers. The NIH web site does not offer personalized medical advice to individuals about their condition or treatment. The resources on this site should not be used as a substitute for professional medical care, and patients are urged to work with their medical care providers for answers to personal health questions. For general medical questions, patients are encouraged to visit the Health Information (http://www.nih.gov/health/) section of the NIH web site. MEDLINEplus at http://www.nlm.nih.gov/medlineplus/ is another useful source for obtaining information on various conditions, diseases, and wellness programs. The site also has a medical encyclopedia, a medication guide for consumers (*USP DI Advice for the Patient*), a glossary, medical dictionaries, health-related directories, special NIH programs, and other resources. For questions relating to specific foods, or prescription, or over-the-counter drugs, the Food and Drug Administration's (FDA) web site http://www.fda.gov/ is recommended. Healthfinder at http://www.healthfinder.gov/ contains valuable information on choosing quality medical care. Also, toll-free medical Information Hotlines may be found at http://www.nih.gov/health/infoline.htm.

Extensive information resources are available directly from the Institutes and Centers that comprise the NIH. For example, the National Cancer Institute provides extensive cancer-related information through its CancerNet program (http://cancernet.nci.nih.gov/) and the Cancer Information Service (1-800-4-CANCER). This includes cancer statistics, cancer information for patients, and access to a bibliographic cancer database (Cancerlit) and the cancer information database PDQ® (Physician Data Query). Health information and clinical guidelines are also available from other Institutes and Centers. The National Heart, Lung, and Blood Institute, for example, provides information for patients, healthcare professionals, and the general public about various vascular, heart, lung, blood, and sleep disorders (http://www.nhlbi.nih.gov/health/ index.htm). Authoritative national clinical guidelines pertaining to asthma, cholesterol, chronic obstructive pulmonary disease, hypertension, obesity, and others are also available (http://www.nhlbi.nih.gov/guidelines/ index.htm). Most of these NIH guidelines and those from other reputable organizations may also be accessible from the National Guideline Clearinghouse (http://www.guideline.gov/). Information regarding dietary supplements and herbal products is available from the National Center for Alternative and Complementary Medicine (http://nccam.nih.gov/). These include fact sheets, consensus reports, and the Complementary and Alternative Medicine Databases (CAM).

NEWS AND EVENTS

The News and Events page (http://www.nih.gov/news/) is the source for NIH news, calendars of events, press releases, special reports, and information about NIH-sponsored events—including events of interest to the media and those available through NIH VideoCasting. Information regarding NIH Consensus Development Conferences and NIH State-of-the-Science Conferences can be obtained via http://odp.od.nih.gov/consensus/default.html. NIH clinical alerts and advisories (http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html) are provided to expedite the dissemination of findings from NIH-funded clinical trials where such release could significantly affect morbidity and mortality. The NIH Calendar of Events, or "Yellow Sheet," is located at http://www.nih.gov/news/calendar/nihcalendar.htm. It lists NIH-sponsored meetings and other meetings of interest to scientists, healthcare professionals, and the general public. It is updated daily, and the listed meetings are free and open to the public.

GENERAL INFORMATION

The e-mail and phone directory for NIH employees may be found at http://directory.nih.gov/.

Information about employment opportunities and summer internships at NIH may be found at http://www.nih.gov/about/index.html#employ.

The emergence of several abuses of the research process has generated some confusion about which office handles what type of abuse within the Department of Health and Human Services (HHS). The attached document (http://ori.dhhs.gov/) was prepared to help clarify the matter.

Information regarding Freedom of Information Act (FOIA) requests may be found at http://www.nih.gov/icd/od/foia/index.htm.

REFERENCE

1. National Institutes of Health Home Page (http://www.nih.gov).

PROFESSIONAL RESOURCES

National Library of Medicine

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INTRODUCTION

The National Library of Medicine (NLM) is the world's largest biomedical library containing nearly 6 million books, reports, journals, photographs, manuscripts, and computer images.[1,2] Located on the campus of the National Institutes of Health in Bethesda, Maryland, this national resource houses material on the topics of medicine, healthcare, and biomedical technology. Information on physical, life, and social sciences is also a part of the NLM. In addition to storing this immense collection of medical literature, the NLM operates more than 40 online databases,[3] the most popular of which is MEDLINE, the world's largest up-to-date online collection of biomedical citations.[1,4]

HISTORY

The NLM dates back to 1836 as a collection of medical texts in the office of the United States Army Surgeon General.[1] Publishing of the *Index Medicus* (a printed, monthly subject/author guide to medical journals) commenced in 1879 under the direction of John Shaw Billings. By 1910, this once-modest library of the Surgeon General's office had grown to be the largest medical library in the world. The National Library of Medicine became the official name of this collection in 1956 when the United States Army transferred the oversight of the library to the U.S. Public Health Service.

The goal of the NLM has remained constant—to increase the availability of medical literature worldwide. In the past 50 years the NLM, working to achieve this goal, has contributed tremendously to the biomedical field (Table 1). In 1971, the NLM launched MEDLINE, an index to biomedical articles, to support the information needs of healthcare professionals.[4,5] Originally used only by trained librarians, MEDLINE became directly accessible to healthcare professionals in the 1980s.[5] During the past two decades, the NLM expanded the topics of its databases and now includes a variety of databases on AIDS, cancer, research, clinical trials, chemical information, toxicology, and ethics (Table 2).

With the arrival of the World Wide Web and its ability to facilitate global communication came the opportunity to expand the services of the NLM. In 1997, the cumbersome methods of searching the MEDLINE database were replaced with user-friendlier search systems, namely Internet Grateful Med and PubMed. Moreover, searching via these resources was now free. These search systems fueled a 10-fold increase in the use of MEDLINE to 75 million searches annually.[6] Today, more than 250 million MEDLINE searches are performed each year.[1] In addition to MEDLINE, users can access almost any of the NLM databases from the NLM health information page, http://www.nlm.nih.gov/hinfo.html.

MEDLINE

MEDLINE is a bibliographic database that contains more than 11 million references to journal articles from 4300 national and international biomedical journals, covering the period from 1966 to the present.[1] Types of journals indexed in MEDLINE include pharmacy, allied health, nursing, medicine, veterinary medicine, dentistry, preclinical science, and life science journals. Each week, nearly 8000 reference citations, created by the NLM and its partners, are added to the MEDLINE database.

As Yahoo! and Excite are to the World Wide Web, PubMed and Internet Grateful Med are to MEDLINE (see Tables 2 and 3). Although both of these latter search services access MEDLINE, the two differ in the way searches are conducted.[5] (Search strategies and instructions for PubMed and Internet Grateful Med will not be included within this article because this information can be found in detail on their respective Web sites). Each service offers access to different databases. Accessing each database is simple and there is a direct link on the PubMed home page to Internet Grateful Med and vice versa. Results from searches in both services offers direct links to full-text articles from more than 800 participating

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006185

Table 1 Highlights of the National Library of Medicine since 1956

Computerization of the *Index Medicus* and the development of MEDLINE
Provision of free access to the MEDLINE database
Development of
The NLM Web site (www.nlm.nih.gov), which is a portal to information on its healthcare databases, news, research programs, and library programs
PubMed, a free NLM database search service
MEDLINE*plus*, a Web site for consumer health information
the National Network of Libraries of Medicine
Development and implementation of an integrated library catalog (LOCATOR*plus*) that can be searched through the Internet
Creation of
A grant program, to support research in medical informatics and in biotechnology and health information
The Toxicology and Environmental Health Information Program, to facilitate governmental and nongovernmental literature (this program operates TOXNET, http://toxnet.nlm.nih.gov/)
The Lister Hill National Center for Biomedical Communications (http://lhncbc.nlm.nih.gov), which oversees NLM research and development
The National Center for Biotechnology Information (NCBI, www.ncbi.nlm.nih.gov), which is responsible for the databases that contain DNA and protein sequences, genome mapping data, and 3-D protein structures.
The National Information Center on Health Services Research and Health Care Technology
PubMed Central

(Adapted from Ref. [1].)

journals. The services offered by PubMed and Internet Grateful Med are updated continually, and the reader is encouraged to visit their Web sites often to check out new features.

The NLM developed PubMed as a user-friendly search tool to explore MEDLINE. For each citation listed in a search result, the user has the option to click on "Related Articles," which takes the user to a listing of additional citations that are related to the search topic. Additionally, PubMed offers access to publisher Web sites for full-text articles, a citation matcher (service that assists a user in finding a complete citation), and access to the molecular biology databases of the NCBI. One of the newest features of PubMed is called "Cubby," a page on the site that allows the user to store a search and update it in the future (users need to register for this free service). AIDSLINE soon will be added to PubMed.[7] A user can search MEDLINE and 14 other NLM databases (e.g., AIDSLINE, AIDSDRUGS, TOXLINE) via Internet Grateful Med. Since 1998, Internet Grateful Med searches MEDLINE using the PubMed retrieval engine.[3]

Once a MEDLINE search has been done via either PubMed or Internet Grateful Med, the user has the option of ordering listed articles from Loansome Doc®, an international, online, article-ordering service from the National Network of Libraries of Medicine.[1] Before users can place an order, however, they must identify an "Ordering Library," then register using the Loansome Doc registration page. Although there is no fee for using Loansome Doc, there is a charge for copies of articles.

IMPLICATIONS FOR PHARMACY PRACTICE AND RESEARCH

The NLM has brought about important changes to pharmacy practice and research. By searching MEDLINE and its other databases, pharmacists, pharmacy researchers, and pharmacy students can find answers to clinical questions, seek help in decision making, obtain information to support research, expand their knowledge on a certain drug topic, and explore and obtain available data to prepare educational tools for colleagues, students, patients, and consumers.

When a pharmacist or pharmacy student has a clinical question, a good place to begin seeking an answer is the medical literature. MEDLINE is used often to solve clinical questions;[10,11] rare clinical conditions have been diagnosed from the results of a MEDLINE search.[4] Some hospitals or medical libraries offer search systems that will search medical literature from MEDLINE and other sources, such as *Best Evidence* and the Cochrane Library.[10] Other sources for clinical decision making by pharmacists include clinical practice guidelines. The NLM offers the Health Services/Technology Assessment Text (HSTAT),[12] a free resource that allows users to access full-text evidence reports, clinical practice guidelines and consensus statements (such as those from the NIH and the AHCPR), technology assessments, and other documents useful in healthcare decision making. One other interesting resource made available online by the NLM is the Online Mendelian Inheritance in Man™ Web site.[13] This site, primarily for healthcare professionals, is a searchable database of human genes and genetic disorders.

Aiming to bring the benefits of advanced technology to the healthcare profession, other NLM programs, like the Visible Human Project, offer new opportunities to study human anatomy and options to further medical research. The Visible Human Project[14,15] is essentially a database of electronic transverse CT, MRI, and cross section images from an entire female and male human cadaver.

Table 2 Primary databases of the National Library of Medicine

NLM database	URL	Description
MEDLINE	Search via PubMed or via Internet Grateful Med (below)	Can be searched using NLM's controlled vocabulary, MeSH, or by author name, title word, text word, journal name, phrase, alone or in combination. The result of a search is a list of citations (including authors, title, source, and often an abstract) to journal articles.
PubMed	www.ncbi.nlm.nih.gov/PubMed	Launched in 1997 to provide free access via the World Wide Web to MEDLINE. Also links to molecular biology databases.[a]
Internet Grateful Med	www.igm.nlm.nih.gov	Launched in 1997 to provide free access via the World Wide Web to MEDLINE. Also provides access to 14 other NLM databases.[a]
PubMed Central	www.pubmedcentral.nih.gov	System launched in 2000 to make available life science research results online. Provides free full-text articles from its own journals; also provides links to free full-text articles from peer-reviewed journals (*nih.gov*).
MEDLINE*plus*	http://medlineplus.gov	Site aimed at answering health-related questions of the consumer. This site contains information on hundreds of diseases, conditions, and wellness issues and includes directories of physicians, hospitals, and medical libraries.
ClinicalTrials.gov	http://clinicaltrials.gov	Site targeted toward consumers and healthcare professionals that provides easy access to information on nearly 5000 clinical trials for a wide range of diseases and conditions.
TOXNET	http://toxnet.nlm.nih.gov	User-friendly Web site that allows searching of a cluster of bibliographic and factual databases with information on toxicology and environmental health. Includes the Hazardous Substances Databank (HSDB), with detailed information about 4500 chemicals, and TOXLINE, containing >3 million citations to journal articles and technical reports.

[a]See Table 3.
(Adapted from Refs. [1, 3, 7–9].)

Table 3 Choosing PubMed versus Internet Grateful Med

Both search services provide functions for helping create and refine searches, including access to hundreds of thousands of biomedical terms from the NLM Unified Medical Language System.
In general, the choice of which Web site to use is personal.
Use PubMed when you need:
- An exhaustive search (i.e., 1996 to present)
- Genetics research information
- Information from a textbook[a]

Use Internet Grateful Med when you need:
- Access to any of the NLM AIDS databases or databases other than MEDLINE
- Articles from 1963 to 1965 (OLDMEDLINE)

[a]This is a "future feature." At the time of this printing, only one book is available on the PubMed Web site. PubMed is working with book publishers to be able to offer a larger selection of textbooks for the user to search online.
(Adapted from Refs. [5] and [7].)

Several applications are offered on the Web site to allow the user to view the images from the project. Although these data sets are free, the user must have a license from the NLM to view and use images from the site.

Pharmacists, with their knowledge of drugs and diseases, may have a tremendous impact on the healthcare team if they possess the necessary skills required to search NLM databases and interpret search results. Even with the amazing technology of the Internet and with the enormity of accessible medical databases, research shows that physicians still do not make use of the information retrieval systems like MEDLINE.[16] With the arrival of high-speed Internet connections, Loansome Doc, and the increased number of journal publishers offering full-text articles online, pharmacists quickly can obtain articles from the results of their searches. This new technology saves mounds of time spent in the library searching for articles—which potentially translates into more time to assist other members of the healthcare team and for patient care.

TELEMEDICINE AND ELECTRONIC PUBLISHING: CURRENT FOCI OF THE NLM

Telemedicine and electronic publishing are top priorities for the NLM. Providing timely, quality healthcare to residents in remote and rural locations via telemedicine is a technological advance that we would not have without the Internet or without funding by organizations like the NLM. Telemedicine is the "transfer of electronic medical data (i.e., high-resolution images, sounds, live video, and patient records) from one location to another."[17] Currently, the NLM is one of six strategic partners that provide support to the Telemedicine Information Exchange,[17] an organization that keeps track of all that is happening worldwide in the area of telemedicine, including operating a database of nearly 10,000 citations regarding this topic. The NLM is funding at least 19 projects under the National Telemedicine Initiative to determine the feasibility, costs, and efficacy of telemedicine compared with conventional care.[18]

In terms of electronic publishing, the NLM launched PubMed Central this year in an effort to reduce the time from article submission to publication and to increase the dissemination of new information in the life sciences.[19,20] PubMed Central eventually will contain two types of data depositories: The first will be peer-reviewed content from journals that will partner with NLM to make their content available free to the public; and the second depository will contain articles submitted directly by authors. Ideally, PubMed Central would increase the options for researchers and academicians to publish their research. This is a very new concept in medical publishing and it will be exciting to watch how it takes shape in terms of the quality of research articles submitted and the way in which the healthcare community embraces this new source of information.

SUMMARY

The NLM is an organization devoted primarily to improving the access by health professionals, researchers, students, and consumers to the worldwide biomedical literature. Although MEDLINE is the most recognized and most frequently used[4] service of the NLM by the pharmacy community, the NLM serves also to create and expand databases and databanks to explore new communication technologies in order to improve the organization and use of biomedical information, to support a national network of local and regional medical libraries and to educate users about available sources of information so that they may conduct their own research concerning medical topics.[1]

CONTACTING THE NLM

The NLM is located at 8600 Rockville Pike, Bethesda, Maryland, U.S.A., 20894. To contact the NLM, send an e-mail to custserv@nlm.nih.gov; call (888) FIND-NLM, (888) 346-3656, (301) 594-5983; or view its Web site at http://www.nlm.nih.gov. For information about the holdings of the NLM, visit LOCATOR*plus* at www.nlm.nih.gov/locatorplus/.

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PROFESSIONAL DEVELOPMENT

Neurology Specialty Pharmacy Practice

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INTRODUCTION

Neurology specialty pharmacy practice involves the provision of pharmaceutical care to patients with neurological diagnoses in collaboration with neurologists and other members of the neurology team. Although it has many similarities with other clinical pharmacy specialties, there are unique aspects and strategies employed that warrant discussion. The neurological deficits themselves make it sometimes more challenging to obtain information from the patient, and a relative paucity of well-studied treatments for many neurological illnesses poses significant challenges. Consensus statements, whether national or regional, are important sources of treatment information in this specialty.

Historically, neurology pharmacy specialists have concentrated on the most medication-intense subspecialty within neurology, which is epilepsy. However, the 1990s saw an explosion in the number of new therapies for neurological illness, both for previously untreatable conditions (e.g., amyotrophic lateral sclerosis, acute stroke) and as additions to the therapeutic armamentarium in already treatable conditions (e.g., epilepsy, Parkinson's disease). The twenty-first century ushers in a continued intense interest in the development of novel therapies for nervous system diseases and steadily broadening opportunities for the pharmacy specialist in neurology.

APPROACH TO THE NEUROLOGIC PATIENT

Pharmacotherapy History

The importance of an accurate pharmacotherapy history to the neurology pharmacy specialist cannot be overemphasized. When integrated with information from the community pharmacy, the outpatient clinic, and the laboratory, a careful assessment of the patient's recollection, together with that of family members, can often expedite implementation of effective therapy and prevent adverse drug effects. The pharmacotherapy history includes assessments of the following:

1. Current problems (History of present illness? Relationship to drug therapy?).
2. Past medical history (Validate chart, probe in more depth regarding relevant history.)
3. Current prescribed medication and indication and duration for each, including physician office samples.
4. Current nonprescription medication and nutritional/herbal products with indications and durations.
5. Assessment of current therapy efficacy (Frequency and severity of headaches? Number of seizures? Improvement of tremor?).
6. Assessment of adverse effects (Ataxia? Drooling? Dyskinesias?).
7. Past medications, efficacy assessment, and reasons for discontinuation, with dates.
8. Known adverse reactions to medication, including allergies and sensitivities, with descriptions of each.
9. Adherence assessment.
10. Insurance assessment (Does patient pay for medication?).
11. Targeted questions depending on suspected diagnosis (e.g., aspirin use in stroke patients; grapefruit juice in elderly patient with hypotension and nifedipine, antipsychotic or antiemetic medication in Parkinson's disease).
12. Name of community pharmacy where patient obtains medications.

REVIEW OF SYSTEMS

A complete discussion of the review of systems is included elsewhere.[1] In reviewing the systems of a

DOI: 10.1081/E-ECP 120006230

neurological patient, depending on the patient's diagnosis, some systems should receive special attention. Some examples of potential neurology-associated problems that can be detected by a review of systems are as follows:

1. *Vital signs*: Are there any abnormalities that could be drug related? For example, sympathomimetics or stimulants may cause hypertension that could increase stroke risk. Temperature, heart rate, and blood pressure are important therapeutic monitoring parameters for medications such as antihypertensives, corticosteroids, and stimulants. Weight gains or losses can be attributed to some medications, such as valproic acid and tricyclic antidepressants for weight gain or topiramate for weight loss.
2. *Cardiovascular*: Does the patient have atrial fibrillation, a coronary artery disease history, or hyperlipidemia increasing stroke risk? Could orthostatic hypotension be due to medications for Parkinson's disease treatment? Is a medication such as amantadine causing peripheral edema?
3. *Pulmonary*: Does the patient require medications for pulmonary disease that may affect neurological functioning such as beta agonist-induced tremor? Could a medication such as beta-blockers prescribed for essential tremor cause deterioration of pulmonary function? Could an acute pulmonary illness such as pneumonia be contributing to delirium? Does the patient have a history of pulmonary embolism that may indicate a predisposition to thromboembolic disorders? Is the patient a current or past smoker, contributing to stroke risk or migraines?
4. *Fluid/electrolyte/nutritonal status*: Does the patient require nutritional supplementation as is the case for folic acid during pregnancy to prevent neural tube defects, a vitamin B_{12} deficiency-associated peripheral neuropathy, or a disease-associated inability to ingest adequate nutrition (amyotrophic lateral sclerosis or debilitating stroke)? Does the patient have adequate hydration (dehydration affects cerebral blood flow)? Are feeding tubes present, requiring special dosing form considerations? Is the patient hypoalbuminemic, which may impact dosing adjustments for highly protein-bound medications? Is the patient on the ketogenic diet for seizure control that requires careful examination of all carbohydrate sources, including medications?
5. *Renal*: Is it necessary to adjust doses for poor renal function?
6. *Hepatic*: Is there evidence of hepatic dysfunction that may require dosing adjustment of antiepileptic agents or statins?
7. *Endocrine*: Diabetes increases risk of stroke, may worsen stroke outcomes, and causes peripheral neuropathy. Thyroid disorders may contribute to mental status changes. Is the patient postmenopausal, increasing stroke risk?
8. *Hematology*: Does the patient have a blood dyscrasia attributable to antiepileptic drugs or other medications? Is the patient hypercoagulable, causing an increased risk of stroke? Does the patient have any particular bleeding risk that limits antiplatelet drug use?
9. *Gastrointestinal*: Does the patient have nausea, vomiting, diarrhea, or constipation caused by a medication or neurological disease state?
10. *GU/reproductive*: Because of neurological disease, some patients must use a urinary catheter, predisposing them to urinary tract infections and requiring frequent antibiotic use. What form of contraceptive does the patient use, if any? Oral contraceptives may be less effective with antiepileptic drugs or may contribute to headaches or stroke risk in a smoker. Is the patient pregnant or breastfeeding, thus prompting close examination of medication use? Stroke risk is also increased in the postpartum period.
11. *Musculoskeletal*: Does the patient have muscular pain that could be caused by statins? Does the patient have muscular spasms or central spasticity requiring an antispasmodic? Does the patient complain of arthritic joint pain? Are tension headaches a problem? Does the patient have a tremor that could be attributed to medication use such as lithium, valproic acid, or beta agonists? Does the patient have weakness that could be due to medication use, underuse, or overuse (e.g., pyridostigmine underuse, antispasmodic overuse)?
12. *Neurological*: Discussed later.
13. *Psychological*: Does the patient have undertreated depression, schizophrenia, or bipolar disorder that may complicate neurological disease treatments? Could psychotic symptoms be caused by neurological illnesses such as diffuse Lewy body disease or Huntington's chorea? Could hallucinations be caused by medication use such as dopaminergic agents? Does the patient require medication for attention-deficit disorder?

14. *Skin*: Check for drug related skin abnormalities (rashes). Know the patient's baseline skin conditions before a new medication is started.
15. *EENT*: Does the patient have gingival hyperplasia caused by phenytoin? Does the patient have thrush or stomatitis that could be caused by a medication? Does the patient have dry eyes caused by an anticholinergic medication effect? Has the patient noted hair loss that could be due to valproic acid? Is the patient able to swallow solid dosage forms. Does the patient complain of vertigo that could be medication induced?

Pharmacist's Targeted Neurological Exam

The pharmacist need not rely on the physician's record of the neurological examination to monitor the safety and effectiveness of the prescribed therapy. A brief (5-minute), targeted neurological exam can be performed on each patient and is described in Table 1. This examination is derived from the complete neurological examination, performed by a physician in the diagnosis of neurological disease, and is designed to provide the pharmacist with data necessary for the design, implementation, and monitoring of pharmaceutical care plans.

INPATIENT NEUROLOGY SPECIALTY PRACTICE

The clinical pharmacist specialist performs many functions for the hospitalized neurological patient. In addition to performing the pharmacotherapy history, review of systems, and neurological exam on new admissions to formulate a care plan, the pharmacist monitors the patient's progress and documents the therapeutic outcomes. Table 2 lists the common inpatient neurological diagnoses with the medications and monitoring parameters used by clinical pharmacists.

One of the most important contributions the pharmacist can make to the care of the patient is the detailed instructions and medication education provided prior to discharge to the patient, family, or caregiver. Identifying barriers to optimal use of outpatient medications and creating a viable circumvention plan (e.g., indigent programs from pharmaceutical companies, prescription of formulary items only, streamlining regimen) begins at admission and ends with the final discharge interview.[2] Follow-up phone calls at 48 hours to answer questions are helpful to the patient/caregiver who is often overwhelmed during hospitalization and thinks of questions when faced with the challenge of correctly following the prescribed medication after discharge.

On a more global scale, the neurology pharmacy specialist working in an inpatient setting is involved in

Table 1 Pharmacist's targeted neuro examination

Domain	Assessment	Diseases/therapies monitored
Mental status	Greeting the patient daily: Does the patient remember you? Does the patient know where he/she is? Assess alertness, speech, memory, and ability to communicate and compare with baseline. Mini Mental Status Examination may be required for insurance approval of some therapies for Alzheimer's disease.	Dementias, delerium, stroke, encephalopathies, agents that cause sedation and/or confusion
Cranial nerves	Note facial tone and symmetry, gaze preference, and ptosis; check for nystagmus by having patient follow object across visual field; engage in conversation to assess for slurred speech.	Myasthenia gravis (ptosis), Parkinson's disease (masked facies), stroke (palsy), antiepileptic drug therapy (nystagmus, slurred speech)
Motor function	Assess handshake for ability to lift arm against gravity and motor control; move toward target (your hand); assess tremor (resting, action, and postural) of hand; assess grip strength. Ask patient to lift leg off bed. Observe for dyskinesias.	Stroke (arm and leg weakness), Parkinson's disease (tremor, bradykinesia, rigidity, dyskinesias), essential tremor
Sensory function	Touch patient on both arms/legs and assess symmetry; inquire about paresthesias.	Stroke, neuropathy (diabetes, HIV, drug-induced)
Gait	Do not test in hospitalized patient (ask the patient if he/she has been walking); observe patient walking normally, heel-to-toe, and turning.	Stroke, vertigo, Parkinson's disease, antiepileptic drug toxicity

Table 2 Common inpatient neurology diagnoses

Diagnosis	Interventions	Monitoring
Ischemic stroke	TPA, heparin, ASA, clopidogrel, ticlopidine, dipyridamole and aspirin, warfarin, surgery	Neurological worsening, bleeding, PT/APTT, INR, CBC
Back pain	Analgesics, surgery, antibiotics if infectious	Pain, sedation, cultures/sensitivites
Bell's palsy	Steroids, acyclovir, artificial tears and lubricants	Weakness, paresthesias
Guillain barre	Plasmapheresis, IVIG	Hemodynamics, respiratory status, renal function
Headache	Surgery if SAH, IV DHE, analgesics, triptans	Pain, sedation, neurological status
Multiple sclerosis	Methylprednisolone, beta interferons, glatiramer acetate, antispasmodics, anticholinergics	Weakness, paresthesias, vision, injection technique
Seizures	Antiepileptic agents	Seizure activity, CNS side effects, respiration, EEG
Subarachnoid hemorrhage	Surgery, BP control, nimodipine, volume expansion, sedation, seizure prophylaxis, stool softeners, ventricular drainage	Neuro status, BP, hydration status, EKG, ICP
TIA/vertebrobasilar insufficiency	Surgery, antiplatelets, heparin/warfarin	Neuro status, bleeding, platelets, BP/hydration, aPTT, INR
Weakness, acute generalized	Depends on final diagnosis	Drug induced? Infectious?

Key: TPA, tissue plasminogen activator; ASA, aspirin; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; CBC, complete blood count; IVIG, intravenous immune globulin; SAH, subarachnoid hemorrhage; IV DHE, intravenous dihydroergotamine; CNS, central nervous system; EEG, electroencephalogram; BP, blood pressure; EKG, electrocardiogram; ICP, intracranial pressure; TIA, transient ischemic attack.

guideline development (e.g., treatment of hypertension in stroke patients), critical pathway/protocol development,[3] adverse drug reaction reporting, and Pharmacy and Therapeutics Committee new drug evaluations.

OUTPATIENT NEUROLOGY SPECIALTY PRACTICE

The clinical pharmacist positioned in the outpatient setting can also significantly affect patient care. In contrast to the inpatient neurological specialist, the outpatient specialist usually cares for more chronic neurological problems and may develop a long-standing relationship with their patients. The elements of the pharmacotherapy history, review of systems, and neurological exam are the same as previously described for the inpatient setting. Table 3 lists common outpatient neurological diagnoses with the medications used and monitoring parameters used by clinical pharmacists.

Formulating the pharmaceutical care plan is a very important part of the outpatient neurological pharmacists' duties. Special care must be taken to remove barriers to the patient obtaining the required medications. This may involve facilitating refill requests, obtaining insurance or health maintenance organization approvals for nonformulary medications, or requesting patient assistance from pharmaceutical companies for medically indigent patients. Patients determined to be nonadherent to their medication regimen should also be investigated for the cause. This etiology may be as diverse as lack of understanding of the disease state to difficulty tolerating the medication to inability to afford the medication. In most cases, the pharmacist can assist the patient with these barriers to adherence.

In the neurology population, patient medication education is very important as regimens can be very complex and the patient may have communication or comprehension difficulties. The pharmacist may develop educational materials and clear, concise directions for medication adjustments to help patients. Specialized calendars or dosing charts can provide a visual reminder to patients in addition to verbal counseling.

From these basic clinical pharmacy functions, the ambulatory neurological pharmacist may choose to subspecialize in any of the common disease states seen in neurology clinics. In disease states where medication plays an important role in patient care and close monitoring is necessary, the pharmacist can be an essential part of patient management. As previously mentioned, the majority of clinical pharmacist involvement in neurology has been in epilepsy clinics. There are several good re-

Table 3 Common outpatient neurology diagnoses

Diagnosis	Interventions	Monitoring
Epilepsy	Antiepileptic drugs, surgery	Medication serum concentrations, sedation, cognitive abilities, liver function tests, blood dyscrasias, bleeding abnormalities, CNS toxicities, rashes, seizure counts, other drug-specific adverse effects
Headaches (abortive treatment)	Triptans, ergotamines, NSAIDS, opiates, oxygen, Midrin®	Sedation, chest pain, tingling/numbness, pain relief
Headaches (prophylactic treatment)	Beta blockers, calcium channel blockers, tricyclic antidepressants, divalproex sodium, gabapentin	Disease-specific cautions (i.e., beta-blockers and diabetes), blood pressure, heart rate, tremor, medication-specific adverse effects, headache count
Parkinson's disease	Levodopa/carbidopa, dopamine agonists, amantadine, selegiline, COMT inhibitors, anticholinergics, surgery	Dyskinesias, orthostatic hypotension, hallucinations, sedation, anticholineric effects, relief of symptoms
Multiple sclerosis	Beta interferons, glatiramer acetate, glucocorticoids, antispasmodics, amantadine, stimulants, immunosuppressants	Number of exacerbations, self-injection technique, injection site reactions, amount of spasticity, amount of fatigue, CBC and infections (immunosuppressants), medication-specific adverse effects
Alzheimer's disease	Cholinesterase inhibitors, antipsychotics	Mini Mental Status Examination, gastrointestinal complaints, number of hallucinations, liver function tests (tacrine)
Myasthenia gravis	Cholinesterase inhibitors, immunosuppressants	Weakness, fatiguability, diarrhea, drooling, CBC and infections (immunosuppressants)
Ischemic stroke prevention	Antiplatelets, anticoagulation, lipid-lowering agents, antihypertensives, smoking cessation	Signs/symptoms of stroke/TIA or bleeding, INR, serum lipid concentrations, blood pressure, smoking status
Amyotrophic lateral sclerosis	Riluzole, antisecretory medication, supportive care	Weakness, drooling
Peripheral neuropathy	Tricyclic antidepressants, antiepileptic drugs, mexilitine, capsacian	Sedation, anticholinergic effects, blood dyscrasias, arrhythmias, medication-specific adverse effects, pain relief
Chronic pain	Surgery, NSAIDs, opiates, tricyclic antidepressants, antiepileptic drugs	Sedation, pain relief

Key: CNS, central nervous system; NSAIDs, nonsteroidal anti-inflammatory drugs; COMT, catechol-O-methyltransferase; CBC, complete blood count; TIA, transient ischemic attack; INR, international normalized ratio.

ports of these clinics in the literature.[4–8] The reported responsibilities of the clinical pharmacists included taking medication histories, performing directed neurological examinations, ordering laboratory evaluations for monitoring medications, assessing adverse drug reactions, providing medication counseling, and providing pharmacokinetic consultations.

The role of the clinical pharmacist in a specialty headache clinic has been described by Adelman and Von Seggem.[9] This individual obtains medication histories and extensively counsels patients on their medication regimens. In addition, the clinical pharmacist determines changes to the patient's therapeutic regimen to enhance effectiveness and minimize toxicity.

Pharmacists may be involved in a multidisciplinary stroke program with an outpatient component. Here the pharmacist may monitor and adjust anticoagulation treatment and provide safety monitoring for ticlopidine through collaborative care agreements with the prescriber and the patient.[10] Vigilant monitoring of disease states that may contribute to stroke risk such as diabetes, hyperlipidemia, or hypertension with appropriate medication adjustments can also be the realm of the pharmacist. Extensive patient education materials may be necessary, and the clinical pharmacist may want to participate in community education efforts such as stroke screenings.[11]

Other medication-intensive neurological disorders include Parkinson's disease and multiple sclerosis. Al-

though specific pharmacist interventions have not been reported in the literature for these disease states, some opportunities for involvement can be envisioned. For Parkinson's disease, the pharmacist may develop a collaborative relationship with the neurologist and make necessary adjustments to medication regimens in response to patient needs. In this case, the pharmacist would likely develop a specialized set of physical assessment skills, including detailed motor examination. Parkinson's disease-specific diaries and medication regimen handouts could be provided to this population and be used for dosage adjustments. The multiple sclerosis population can also benefit from pharmacist involvement. When disease-modifying therapies such as beta interferons, glatiramer acetate, or immunosuppressants are prescribed, a great deal of patient education must be performed. Patients must understand that these medications are not curative, but slow progression and/or decrease multiple sclerosis exacerbations. In addition, the patient must be instructed in self-injection technique for the parenteral products and monitoring regimens must be established for the immunosuppressants to ensure patient safety. Other issues that the pharmacist may address include therapy for muscle and bladder spasticity, fatigue, sexual dysfunction, pain, and urinary tract infections.

OUTCOMES

Very few examples of outcomes research in neurological pharmacy exist. However, one historical control study determined that the implementation of a pharmacokinetics consultation service in an epilepsy clinic decreased seizure frequency and number of adverse effects compared with the baseline frequency in the 4 months prior to offering the service.[7] A second study conducted in the pediatric epilepsy population described the effect of establishment of a specialty pediatric epilepsy clinic with clinical pharmacy services. Compared with patients seen before the beginning of the clinic, patients seen in the specialty clinic had decreased numbers of antiepileptic drugs and decreased doses of these medications. Frequency of seizures was not examined in this report.[8]

OTHER ACTIVITIES

Most specialists are involved in both clinical and didactic teaching of pharmacy students, residents, and fellows as well as trainees in other programs (resident physicians, nurses, etc.). Many hold faculty appointments at Colleges of Pharmacy and/or Medicine. In addition, pharmacy specialists participate in and conduct clinical and/or basic research in the neurosciences.

GUIDELINES USED IN NEUROLOGY PHARMACY PRACTICE

The following guidelines may be helpful in providing care to neurology patients:[12]

1. Practice advisory: Thrombolytic therapy for acute ischemic stroke. American Academy of Neurology, 1996 (5 pages).
2. Intravenous immunoglobulin preparations. University Health System Consortium, 1999 Mar (216 pages).
3. Second report of the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). National Heart, Lung, and Blood Institute (U.S.), 1993 Sept (Reviewed 1998) (169 pages).
4. Sixth ACCP consensus conference on antithrombotic therapy. American College of Chest Physicians, 2001 (20 pages).
5. Practice advisory on selection of patients with multiple sclerosis for treatment with Betaseron. American Academy of Neurology, 1994 (reviewed 1998) (4 pages).
6. Sixth report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute (U.S.), 1997 Nov (33 pages).
7. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. American Psychiatric Association, 1996 Dec (93 pages).
8. An Algorithm (Decision Tree) for the Management of Parkinson's Disease: Treatment Guidelines. Neurology 1998; 50 (suppl 3) S1–S57.
9. PRN Opinion Paper: The Ketogenic Diet. *Pharmacotherapy* 1999; 19:782–786.

NETWORKING AND EDUCATIONAL OPPORTUNITIES

Neurology pharmacists have formal networking and educational opportunities at professional pharmacy orga-

nizations (American Society of Health-System Pharmacists, American College of Clinical Pharmacy) and within the confines of neurology subspecialty groups (American Epilepsy Society). In addition, stand-alone groups of clinical specialists, usually in collaboration with psychiatry specialists (College of Psychiatric and Neurologic Pharmacists), develop and offer high-quality, intensive continuing education several times per year in the United States. The introduction of electronic communication has facilitated the exchange of clinical experiences and information via list servs and e-mail directories available on the Internet.

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12. see www.guidelines.gov.

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Nontraditional Pharm.D. Programs

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INTRODUCTION

In 1989, the American Council on Pharmaceutical Education (ACPE) announced its intent to accredit only Doctor of Pharmacy (Pharm.D.) degree programs beginning in the year 2000. Not surprisingly, the creation of a new entry-level degree generated significant controversy. Initial concern focused on the potential impact that two levels of pharmacy practitioner (i.e., baccalaureate vs. Pharm.D.) would have on the profession. Understandably, many baccalaureate pharmacists were particularly concerned about their ability to successfully compete against future graduates in the professional marketplace. Early attempts to resolve the issue included discussions of potential degree transfer mechanisms for baccalaureate pharmacists.[1] For example, the National Community Pharmacists Association (NCPA), formerly known as the National Association of Retail Druggists, responded by issuing a nonacademic Pharmacy Doctor (PD) degree to any association member for a nominal fee. However, as practitioners began to understand the paradigm change espoused by pharmaceutical care and to accept their new roles as vital health care providers, the need for programs that could significantly enhance knowledge and skills gradually overrode the impulse to grandfather degrees.

BACKGROUND INFORMATION

The nation's three largest pharmacy practitioner organizations again addressed the issue in 1991.[2] In a consensus statement released by the American Pharmaceutical Association, the American Society of Health-Systems Pharmacy, and the National Community Pharmacists Association, an entry-level Pharm.D. degree that would prepare pharmacists as generalist practitioners rather than specialist practitioners was strongly endorsed. In addition, the joint statement endorsed the concept of a degree transfer process for current baccalaureate degree practitioners to avoid even the appearance of two distinct practitioner levels. Although never accomplished, the organizations further proposed developing an institute for granting "Pharm.D. equivalency" certificates for baccalaureate practitioners whose colleges of pharmacy do not develop a degree transfer process.

Finally, in 1996, a National Association of Boards of Pharmacy (NABP) Task Force released their report entitled, *Development of an Equitable Degree Upgrade Mechanism.* The task force defined general criteria for pharmacy schools intending to develop a uniform approach to the delivery of nontraditional Pharm.D. (NTPD) programs. These consisted of four essential characteristics for NTPD programs:

- Assessibility—a competency-based process (anchored to NAPLEX endpoint competencies) to be conducted by a committee of faculty and practitioners.
- Accessibility—defined as a practical, nondisruptive program that will not require the applicant to relocate or significantly interfere with his or her practice.
- Academic soundness—defined as a documented evaluation that does not disrupt or compromise accreditation standards.
- Affordability—a program that can be offered to applicants at a reasonable cost and may be completed in a timely manner (e.g., 36 semester hours).

It is within this general context that schools and colleges of pharmacy have attempted to balance the feasibility issues as voiced by the profession with the academic standards and endpoint competencies expected of doctoral-level practitioners. Although NTPD programs existed prior to the landmark ACPE decision to mandate entry-level Pharm.D. practice requirements, this decision and its resulting controversy have directly influenced the rapid growth and innovative approaches to NTPD curriculum delivery. Experimentation in curricular delivery methods has emerged and continued efforts are essential.[3–8] This report will attempt to efficiently summarize the emerging educational approaches and provide an overview of the NTPD programs currently in operation.

DOI: 10.1081/E-ECP 120006358

Table 1 Admission requirements for nontraditional Pharm.D. programs

School/college	Enrollment	Maximum time to complete[b] (yr)	Web site URL	Cost[c]
Samford (Alabama)	Discontinued in 2001[a]	3	http://www.Samford.Edu/schools/pharmacy/ntpd/ntpd.htm	$$$$
Auburn (Alabama)	Open	6	http://pharmacy.auburn.edu/nontrad/	$$
Arkansas	Open	5	www.uams.edu/ntpdp	(R) $ (NR) $$$
Arizona	Open[a]	4	No web site	$$$$
Colorado	Open	5–6	http://www.uchsc.edu/sp/sp/programs/prostudies.htm	(R) $$$ (NR) $$$$
Nova Southeastern (Florida)	Open	5	http://pharmacy.nova.edu/	$$$
Florida	Open	7	http://www.cop.ufl.edu/wppd/www.intelicus.com	(R) $$$ (NR) $$$
Georgia (Mercer and University of Georgia)	Restricted	5	http://www.rx.uga.edu/main/home/ntpharmd/index.htm	$$$
Idaho State	Open	6	http://rx.isu.edu/	(R) $ (NR) $$$$
Midwestern (Illinois and Arizona)	Open	4	http://www.midwestern.edu/CCP/nontrad.html	$$$
Illinois–Chicago	Open	4.5	http://www.uic.edu/pharmacy/offices/cco/cco.html	(R) $ (NR) $$$
Purdue	Restricted	7	www.pharmacy.purdue.edu/~ntdpp/	(R) $$ (NR) $$$$$
Iowa	Restricted[a]	5	No web site	$$
Kansas	Open	5	http://www.pharm.ukans.edu/nontrad/ntpd.htm	(R) $$
Kentucky	Restricted	6	www.uky.edu/pharmacy/npo/	(R) $$ (NR) $$$$$
Louisiana at Monroe	In development		http://rxweb.ulm.edu/pharmacy/	
Xavier (Louisiana)	Not admitting	5	http://www.xula.edu/PharmPostBac.html	$$
Maryland	Open	3.5	No web site found	
Massachusetts COP	Discontinued			
Minnesota	Restricted[a]	3–5	http://www.pharmacy.umn.edu/dp4/	$$
Mississippi	Open	5	http://www.olemiss.edu/depts/pharm_school/NTPharmD.pdf	(R) $ (NR) $$$
Missouri–Kansas City	Restricted	5	http://www.umkc.edu/pharmacy/CE.HTML	$$
Montana	Restricted	6	http://www.umt.edu/ccesp/distance/pharmd/	$$
Creighton (Nebraska)	Open	8	http://pharmacy.creighton.edu/spahp/non_traditional/curriculum/pharmacy/curr_async-pprof.asp	$$$
New Mexico	Restricted	6	http://hsc.unm.edu/pharmacy/Nontraditional.htm	$
Albany (New York)	Open	5.5	http://www.acp.edu/Academics/catalog/programs.htm#non-trad	(R) $$$
Arnold and Marie Schwartz (New York)			No web site found	
Buffalo (New York)	Open	5	http://pharmacy.buffalo.edu/programs/ntpharmd/ntprogram.html	(R) $$$$ (NR) $$$$$

(Continued)

Table 1 Admission requirements for nontraditional Pharm.D. programs (*Continued*)

School/college	Enrollment	Maximum time to complete[b] (yr)	Web site URL	Cost[c]
North Carolina	Open	3	http://www.pharmacy.unc.edu/xpharmd/index.html	(R) $$
North Dakota State	Restricted	6	http://www.ndsu.nodak.edu/instruct/hanel/pharmacy/ntp_let.htm	$$$
Ohio Northern	Open	5	http://www.onu.edu/pharmacy/ntpd/default.asp	$$$$$
Ohio State	Open	6	http://www.pharmacy.ohio-state.edu/ntpd/	$$$
Oklahoma (Southwestern Oklahoma State University and Oklahoma University)	Not admitting[a]		No web site found	
Duquesne (Pennsylvania)	Open	5	http://www.duq.edu/pharmacy/Programs/non-traditional.html	$$$
Philadelphia (Pennsylvania)	Open	5	http://www.usip.edu/graduate/flex	$$$$$
Wilkes (Pennsylvania)	Start Fall 2001		No web site found	
Temple (Pennsylvania)	Discontinued			
Rhode Island	Discontinued			
South Carolina	Not admitting[a]		No web site found	
South Dakota	see Univ. Minnesota			
Tennessee	see Univ. Kentucky			
Texas Schools	Restricted	5	http://www.txpharm.org/	$$$
Utah	see Idaho State			
Virginia Commonwealth	Open	2	http://www.pharmacy.vcu.edu/nontrad/index.html	(R) $$$
Shenandoah (Virginia)	Open	4	http://pharmacy.su.edu/Ntdp/index.html	$$$$
Washington (University of Washington and Washington State University)	In-state preferred	5	http://depts.washington.edu/expharmd	(R) $
West Virginia	Restricted	6	http://www.hsc.wvu.edu/sop/academic/	$$$$
Wisconsin	Open	6	www.pharmacy.wisc.edu/ntpd	(R) $$$

(R) = Resident; (NR) = Nonresident.
Relative cost scale: $ = $6–10,000; $$ = $11–15,000; $$$ = $16–20,000; and $$$$ = $21–25,000; $$$$$ > $26,000.
[a]Indicates programs that did not continue after 2000–2001.
[b]Usual time frame for completion—where applicable, maximum time requirement (max.) is presented.
[c]Costs are subject to change and may vary depending on credit load taken or length of time to complete degree requirements.

Only those schools providing nontraditional approaches (i.e., alternative curricular pathway to an on-campus program) are included here, although it is worth noting that several schools still offer traditional on-campus postbaccalaureate Pharm.D. programs.

A general comparison of the admission requirements, didactic coursework, and clerkship curricula is provided for current NTPD programs in Tables 1–3. This information was collected from a review of each program's web site and/or written information. To ensure current and accurate information, verification was attempted using the AACP's Pharmacy School Admission Requirements for 2001–2002[9] and a telephone call to the program, if needed. Nonetheless, many programs are still under development and others are continuing to experiment with new techniques and methodologies to enhance nontraditional learning. Therefore, program requirements and curricula may change quickly and frequently. A web site address (URL) is provided where available, and readers are encouraged to contact the schools for more specific information.

HISTORY AND GOALS

Although the number of programs has grown dramatically in recent years, nontraditional delivery of Pharm.D. curricula began in the early 1980s, long before the issue of entry-level degree requirements was debated. Purdue University began offering off-campus coursework in 1981. Shortly thereafter, the University of Kentucky (1986), the University of Illinois–Chicago (1986), and Idaho State University (1989) implemented nontraditional programs. These early pioneers represent a small group of highly experienced and well-established programs with successful graduation records.

Nontraditional pharmacy education originated because of the recognized need to enhance the knowledge and clinical abilities of practicing pharmacists while allowing them to continue full-time employment. As is discussed in more detail later in this article, the methods used are diverse and have engendered innovative and at times somewhat controversial educational approaches. However, at this point, it is worth emphasizing that doctoral education generally implies and probably demands some level of self-sacrifice. NTPD programs can only hope to minimize this disruption.

The guiding principle in the development of NTPD programs has been the insistence of ACPE that the educational goals and endpoint competencies are identical to those established for traditional on-campus programs. In other words, the use of the term "nontraditional Pharm.D." does not imply a different degree because no true distinction is recognized by ACPE. Only the delivery of that curriculum differs, and institutions are encouraged to formulate different pathways by which accomplishment of curricular outcomes fulfills requirements for the Doctor of Pharmacy degree. Nevertheless, perceptions of a "correspondence course" or "mail order degree" may exist within some sectors of the profession as evidenced by recent commentaries in the pharmacy literature.[10,11] Hopefully, this overview of current NTPD programs will help to dispel any misconceptions or perceived differences between traditional and nontraditional pharmacy education.

ADMISSION REQUIREMENTS

Although admission requirements vary among NTPD programs, the major differentiating factor is open vs. closed enrollment. As indicated in Table 1, open enrollment refers to programs that will accept applications from practicing pharmacists holding licensure in the United States or its territories. In 1990, one-half of the existing nontraditional NTPD programs restricted admission to licensed practitioners within their state or alumni of the school. Currently, only 14 programs have similar admission restrictions.

Programs offering open enrollment often require foreign applicants to provide proof of English language proficiency either through examination (e.g., TOEFL) or on-campus interview. Canadian pharmacists present a unique situation. Only two Canadian colleges of pharmacy offer a postbaccalaureate Pharm.D. option: the University of British Columbia and the University of Toronto. Because of the high demand, many NTPD programs have opened admission to Canadian pharmacists.[12]

As part of the admission process, NTPD programs generally require applicants to provide the following information: proof of licensure, a completed application form, application fee, official college transcripts, and several letters of recommendation. Other admission criteria vary substantially between programs but may include an on-campus interview, satisfactory achievement on minimum competency assessments, satisfactory completion of prerequisite coursework, and/or minimum GPA criteria.

Recently, much attention has been devoted to prior learning assessment (PLA) as a method to award academic credit or advanced level placement for competencies acquired through previous work experience. As is discussed in more detail later in this article, PLA is a useful methodology for decreasing coursework and time requirements. However, it is not a simple process and requires considerable effort by both students and faculty.

DIDACTIC INSTRUCTIONAL METHODS AND COURSE DELIVERY

Virtually all NTPD programs are structured to allow practicing pharmacists to continue working while taking didactic courses on a part-time basis. This is accomplished using a variety of instructional methods, and a description of the relative merits of each is summarized here. These terms are also used in Table 2 to identify the methods used by each NTPD program.

Videotaped Lectures

In addition to facilitating course delivery in the student's own home, the videotape delivery of didactic courses provides several advantages that nontraditional student-practitioners often find desirable. Studying can be tailored to individual work schedules (i.e., rotating shifts, weekends, or on-call schedules), thereby allowing much greater flexibility and a self-directed study program for

those individuals with irregular schedules or other conflicts. In addition, it allows students to "fast forward" quickly through information that may have been acquired previously while allowing "replay" to review new information when needed.

The major disadvantage of videotaped coursework is the inability to interact directly with the instructor or other classmates. However, most programs currently employ the use of supplemental or web-based interactions with instructors or online small group discussions to overcome, or at least minimize, these deficiencies. Occasionally, poor technical quality may substantially impact course delivery and practitioners considering these programs may want to review sample videotapes or discuss this issue with current students.

Distance Learning

Using a variety of available technologies, transmission of live didactic lectures to remote classrooms remains a common vehicle for course delivery. For many practitioners, this format is probably easiest to assimilate because it closely resembles more traditional teaching methods and affords at least some direct student and instructor interaction. A regular class schedule and close geographic proximity to one of the regional transmission sites are the major limitations to distance learning programs.

Web-Based Coursework

Dramatic improvements in computer technology have fostered the development of unique web-based approaches to curriculum delivery. Several programs offer virtually all didactic coursework via the Internet, and nearly all NTPD programs are gravitating toward this new educational tool. Some programs have found it necessary to contract with private corporations to assist with the rather daunting task of redesigning their entire curricula to an online, interactive format.

Web-based didactic coursework generally allows students greater flexibility in determining their own study schedule and may allow easier incorporation of supplemental educational materials (e.g., Internet links to additional information and/or demonstrations). The positive quality of web-based flexibility must be tempered by recognition of technological limitations, however. Many students find themselves feeling isolated and have difficulty coordinating group projects over the Internet.

Even with recent technological improvements, not all web-based coursework measures up to advertised benefits, and significant problems may occur. Slow transmission rates, server malfunctions, and poor utilization of computer capabilities can result in student dissatisfaction and frustration. As with other educational mediums, students should carefully investigate the quality of web-based materials and attempt to validate program claims via inquiries to active students whenever possible. In a speech, Dr. Victoria Roche cautioned against becoming enamored with technology for its own sake.[13] Studies comparing cybercourses and traditional didactic formats are essential to apply the most effective learning strategies in the future.

NTPD program didactic requirements are remarkably similar; the marked differences reported in Table 2 can be accounted for primarily by differences in prerequisite coursework or delivery methods used. Few programs provide a self-paced format and, despite the widespread potential for self-paced curricula, most NTPD programs follow a traditional semester sequence. Thus, flexibility may be an important distinguishing characteristic depending on the self-directed nature, motivation, or family and work demands of individual students. Conversely, self-paced programs tend to be less interactive because students are generally at different points in the curriculum at any given time. They are less conducive to small-group learning activities (e.g., case discussions and interactive projects) and are best suited for practitioner-students that are highly self-directed.

ASSESSMENT OF PRIOR LEARNING

One of the more difficult issues facing nontraditional programs has been the development of methodologies for assessing learning acquired through previous experience. Obviously, daily practice affords a rich environment for continuing education, yet the extent to which individual practitioners use this varies considerably. To address this issue and provide a mechanism for assessing prior learning, many schools and colleges have developed innovative evaluation processes. Portfolio review has become an increasingly popular mechanism in this regard. Under this process, student-practitioners are given academic credit if they can document their ability to perform specific learning objectives. Frequently, this involves describing in significant detail work situations or patient cases that demonstrate the student-practitioner's ability to understand and perform the objective appropriately. Common examples include the following types of information and documentation:

- A statement of career goals.
- A detailed description of current practice activities, including services provided and patient population

Table 2 Nontraditional Pharm.D. didactic coursework

School/college	Didactic coursework (semester credits)[a]	Challenge exams[b]	Portfolio review[b]	Other[b,d]	Self-paced	Delivery methods[c]
Samford (Alabama)	56 (includes clerkships)	No	No			Distance learning by videoconferencing
Auburn (Alabama)	44	✓(20)	✓(20)			Internet, CDs, traditional lectures
Arkansas	21				✓	Internet, videotapes
Arizona	24				✓	AACP Consortium, videotapes
Colorado	35	✓(3)	✓(4)			All Internet-based course delivery
Nova Southeastern (Florida)	31		✓(15)			Distance learning to regional sites, Internet
Florida	27					Videotapes, Internet, 3 days on-campus/ semester
Georgia Schools (Mercer and University of Georgia)	29	✓(21)				Distance learning, videotapes, tele-conferencing, Internet
Idaho State	28	✓(7)		BCPS (10)	✓	Videotapes, Internet
Midwestern (Illinois and Arizona)	35 quarter hours	✓	✓(30)			Evening/weekend classes
Illinois–Chicago	24		✓(3)	BCPS, DI, and Statistics		Internet, web con-ferencing
Purdue	28			Yes	✓	Videotapes, Internet, regional workshop sites
Iowa	29			Recent grads only		Videotapes, Internet, weekend
Kansas	24	✓	✓			All Internet-based course delivery
Kentucky	26	✓(26)	✓(16)	Yes (4)		Videotaped case studies, Internet, interactive patient activities
Louisiana at Monroe		✓	✓			Distance learning, videotapes, Internet
Xavier (Louisiana)	24	✓			✓	Videotapes, Internet
Maryland	24	✓(6)	✓(10)			On-campus and distance learning, Internet
Massachusetts	Discontinued					
Minnesota	26		✓(15)	(15) total curri-culum		Internet with 1 week-end/year on campus
Mississippi	33	✓(32)	✓(2)	BCPS (32)	✓	Problem-based learning format via chat room groups
Missouri–Kansas City	22				✓	Videotapes
Montana	25	✓		BCPS (14)		Internet, one course videotaped
Creighton (Nebraska)	34	✓(9)	✓(9)	BCPS	✓	Converting to Internet-based courses
New Mexico	Two courses (see delivery methods)			BCPS (all didactics)	✓	ASHP Clinical Skills Program and the ACCP Pharmacotherapy Self-Assessment Program (PSAP)

(Continued)

Table 2 Nontraditional Pharm.D. didactic coursework (*Continued*)

School/college	Didactic coursework (semester credits)[a]	Challenge exams[b]	Portfolio review[b]	Other[b,d]	Self-paced	Delivery methods[c]
Albany (New York)	26	✓	✓(8)	Occasionally	✓	Audiotapes
A and R Schwartz (New York)		✓(9)				Weekend/evening classes
Buffalo (New York)	30		✓(12)		✓	Videotapes, Internet, CD and DVD tele-conferences
North Carolina	25	✓	✓			Videotapes, web bulletin board
North Dakota State	37		✓			Uses Colorado didactic program
Ohio Northern	39 quarter hours	✓(16)	✓(16)	16 quarter hours total	✓	Videotapes, computer-based programs
Ohio State	40 quarter hours					Internet-based course delivery
Oklahoma Schools (Southwestern Oklahoma State University and Oklahoma University)	16	✓(4)				Videotapes, weekend/evening classes
Duquesne (Pennsylvania)	28		✓	(4) previous graduate work	✓	Self-directed study, Internet, and 1–3 day workshops
Philadelphia (Pennsylvania)	24	✓(9)				On campus
Wilkes (Pennsylvania)	27					Weekend/evening classes
Temple (Pennsylvania)	Discontinued					
Rhode Island	Discontinued					
South Carolina	Not admitting					
South Dakota	26					Uses Minnesota didactic program
Tennessee	26					Uses Kentucky didactic program
Texas Schools	19–22	✓(7)	✓(7)			Statewide distance learning and Internet-based technologies
Utah	28					Uses Idaho State didactic program
Virginia Commonwealth	18	✓(9)				Internet
Shenandoah (Virginia)	33		✓(8)			Internet
Washington (University of Washington and Washington State University)	Individualized (Max. 66 quarter hours)		✓(8)		✓	Self-study and workshops
West Virginia	30 (26 from Kentucky)					Uses part of Kentucky didactic program—videotapes, CDs, Internet
Wisconsin	24	✓		(4)	✓	Distance learning, Internet workshops, audio-conferencing

[a]Indicates semester credit hours, except where noted.
[b]Maximum credit hours allowable—not necessarily additive for determining total program waivers.
[c]See text for description of delivery methods.
[d]BCPS, Board of Pharmaceutical Specialties Certification (can be used to waive requirements); ASHP—American Society of Health System Pharmacy; ACCP, American College of Clinical Pharmacy.

Table 3 Clerkship requirements for nontraditional Pharm.D. programs

School/college	Required clerkship (week)	Part-time allowed	Credit for prior experience (max. weeks waived)	Completed at student's worksite (max. weeks)
Samford (Alabama)	None, but patient monitoring required for disease modules	Yes	None	Yes, but not all
Auburn (Alabama)	8 (typically)	Yes	Clerkship requirements are individualized	All
Arkansas	16 (4 weeks on-campus)	Yes	None	12 Weeks self-directed study
Arizona	26	Yes	None	Under certain circumstances
Colorado	30	Yes	Portfolio waiver (12)	(15)
Nova Southeastern (Florida)	16	Yes		
Florida	No, patient monitoring required for disease modules	Yes		Yes
Georgia Schools (Mercer and University of Georgia)	18	Yes	Precepted clerkships (6)	(14)
Idaho State	28	Yes	Substitution only	(16)
Midwestern (Illinois)	20 (32 quarter hours)	Yes	Yes	Under certain circumstances
Illinois–Chicago	30 (20 semester credits)	No	ASHP residency (12)	Clerkships must be completed in Chicago
Purdue	28	Yes	(8)	Under certain circumstances
Iowa	35 (28 semester credits)	Yes	(10)	Under certain circumstances
Kansas	20	Yes	(12)	Yes
Kentucky	32	Yes	(4–16)	Yes, but not all
Louisiana at Monroe	TBA			
Xavier (Louisiana)	15 (9 semester credits)	No	(10)	Yes
Maryland	4.5 (total approx. 180 hours)	Yes	Yes	All
Massachusetts	Discontinued			
Minnesota	25	Yes	Yes, maximum 15 credit hr total for didactic and clerkships	One practice enhancement clerkship
Mississippi	24	Yes	30% of clerkship requirement	Optional case management
Missouri–Kansas City	28	Yes	(8)	(4)
Montana	28	Yes	No	All
Creighton (NE)	24	Yes	(8)	(12)
New Mexico	36	Yes	(16)	No
Albany (New York)	25	Yes	(5)	One self-directed rotation
A & R Schwartz (New York)	16			
Buffalo (New York)	36	Yes	(12)	Yes
North Carolina	28	Yes	(12)	Under certain circumstances
North Dakota State	36			
Ohio Northern	24 (30 quarter hours)	Yes	(8) 10 quarter hours	(8) 10 quarter hours
Ohio State	TBA			

(Continued)

Table 3 Clerkship requirements for nontraditional Pharm.D. programs (*Continued*)

School/college	Required clerkship (week)	Part-time allowed	Credit for prior experience (max. weeks waived)	Completed at student's worksite (max. weeks)
Oklahoma Schools	16	Yes		(8–12)
Duquesne (Pennsylvania)	25 (10 credit hours)	Yes	(10) 4 credit hours	Yes
Philadelphia (Pennsylvania)	24	Yes	(8)	
Temple (Pennsylvania)	Discontinued			
Wilkes (Pennsylvania)	16			
Rhode Island	Discontinued			
South Carolina	Not admitting			
South Dakota State	32	Yes		(1)
Tennessee	32	Yes	(16)	
Texas Schools	19–21	Yes	(3)	(9)
Utah	28			
Virginia Commonwealth	30	Yes	(20)	Yes
Shenandoah (Virginia)	24	No	16	Yes
Washington Schools (University of Washington and Washington State University)	Portfolio review determines clerkship requirements	Yes	Yes	Yes, strongly encouraged
West Virginia	28	Yes	3 Clerkships	2 Rotations
Wisconsin	24	Yes	Substitution only	(4)

served; generally, this includes examples of written patient work-ups or care plans that relate to specific educational objectives.

- Documentation (i.e., dates, location, and copies of handouts, etc.) of presentations at pharmacy or other professional meetings.
- Previous educational activities including disease state management programs, certifications, etc.
- Other community or preventative health care activities.

CLERKSHIP REQUIREMENTS

The experiential component presents special challenges for both NTPD programs and students, particularly in rural areas.[14] Although credit for work-related experience and some flexibility in designing the clerkship schedule are offered, the majority of programs require a significant clerkship component, typically 24 to 28 weeks. Because many programs require full-time clerkship training, a temporary leave of absence, use of vacation time or other work arrangements are necessary. Although this frequently imposes financial and personal difficulties, it is perhaps the most important aspect of Pharm.D. education and should be investigated thoroughly to ensure that career goals and objectives are satisfied.

The types of clerkship experiences and time commitment vary considerably among NTPD programs (Table 3). Internal medicine and ambulatory care constitute the core clerkship requirements of many programs, with electives in mental health, pediatrics, geriatrics, and drug information commonly offered. Some programs, such as Idaho State University's NTPD program, offer a capstone rotation during which the student implements and documents the resultant benefits of some aspect of pharmaceutical care at their original place of employment. This serves not only to further the goals of the profession, but also rewards employers for their flexibility and patience by upgrading the level of care at the employment site.

Most programs allow for part-time completion of clerkships. This can be arranged on a half-time basis (e.g., 4 hours per day) or, more frequently, students may complete one 4- or 6-week rotation, followed by returning to full-time work for a period of time. This allows students significant financial flexibility.

Restrictions vary with respect to fulfillment of clerkship requirements at the student's place of employment. Some programs require students to complete as many clerkships as possible outside their normal workplace,

reasoning that exposure to different practice environments and styles will ultimately benefit the student-practitioner. Other programs have taken the opposite approach, and encourage students to complete all experiential rotations in their normal workplace under the construct that this provides an opportunity to enhance the practice setting by practicing pharmaceutical care skills on their own patient population.

Many NTPD programs have simply funneled their nontraditional students through available traditional clerkship sites, whereas other programs have combined traditional sites with the identification and approval of new clerkship venues. The older NTPD programs have the advantage of expanding clerkship opportunities by using nontraditional graduates as preceptors.

Evaluation of clerkship outcomes and competencies are, by nature, much more subjective than their didactic counterparts. This element, combined with the fact that clerkship requirements of traditional, entry-level Pharm.D. candidates often take priority over nontraditional clerkship needs,[15,16] results in the potential for inclusion of clerkship sites with less than minimal qualifications. Some programs have attempted to sidestep the costly and time-consuming process of evaluating and approving off-site clerkships by creating regional sites (satellites) where students congregate at predetermined intervals (usually monthly or at certain times during the semester) for clinical practice assessments via paper case presentations and group interaction. Students are then expected to accumulate direct patient contact experience independently by following patients identified from their workplace. Students from hospital pharmacy environments may encounter no difficulty finding interesting cases to follow; those with pharmaceutical industry or community pharmacy backgrounds will have more difficulty, and run the risk of sacrificing their capstone clerkship experience for the sake of convenience.

UNDERLYING MOTIVATIONAL FACTORS

Pursuit of a doctorate through the nontraditional pathway requires a significant commitment in terms of time, money, and determination on the part of the candidate.[17–19] The motivations behind obtaining a postbaccalaureate Pharm.D. are multifactorial, but can be separated into two broad categories—external or internal.[20,21] External motivations for application to a nontraditional Pharm.D. program include earning a promotion, employer pressure, and concerns about future job security as a result of the shift from BS to Pharm.D. as the sole entry degree. Internal motivation, however, derives from a desire to enhance personal job satisfaction. Examples of internal motivations include a desire to improve clinical skills to optimize patient care, as well as the desire for greater responsibility in making decisions regarding drug therapy. It has been our experience that students who are internally motivated tend to progress faster through the nontraditional Pharm.D. curriculum and have a lower attrition rate compared with those students who are externally motivated.

The motivations of pharmacists interested in pursuing a nontraditional Pharm.D. degree have been surveyed.[20–22] The most important reasons given for seeking a postbaccalaureate degree were improvement of clinical skills, enhanced work quality, and increased personal satisfaction. Kelly et al. surveyed Pennsylvania pharmacists and discovered that the degree of satisfaction with current employment was inversely correlated with likelihood of enrolling in an NTPD program; more than 73% of pharmacists who found their jobs to be "very unfulfilling" stated they would probably apply.[23]

Two surveys of nontraditional Pharm.D. program graduates have assessed the effect of the degree on practice patterns.[6,24] Respondents from both surveys reported spending a significantly greater percentage of their time performing pharmaceutical care (e.g., making therapeutic recommendations, developing treatment plans) and less time dispensing or processing prescriptions compared with their last position as a BS-trained pharmacist. The respondents also reported significantly greater levels of job satisfaction after graduation from their respective NTPD programs.

Dunn et al. surveyed nontraditional Pharm.D. students currently enrolled at the University of Arkansas.[25] The majority of respondents from this survey reported enhancements in self-esteem, pride in their profession, and an elevation in the overall level of pharmaceutical care at their practice site. More than 85% of the Arkansas nontraditional Pharm.D. students stated that they had gained confidence in their ability to provide pharmaceutical care as a result of the program.

DISCUSSION

The information presented in Tables 1–3 is evidence of the commitment, dedication, and concerns of academic pharmacy regarding the facilitation and enhancement of clinical skills and abilities of active practitioners. This is impressive, particularly in light of the limited lifespan anticipated for NTPD programs. As colleges of pharmacy begin to confer the Doctor of Pharmacy degree exclusively, the demand for NTPD programs will inevitably

wane. Given the high costs of starting a NTPD program (both in terms of faculty time and distance learning infrastructure)[4] and the limited time frame to recoup any investment, some universities have developed unique partnerships. For example, the University of Florida has partnered with a private corporation to facilitate delivery of course materials. However, Idaho State University (ISU) has taken a different approach. ISU has entered into a collaborative clinical training agreement with the University of Utah. As a result, ISU benefits from this agreement by bringing additional out-of-state students into its established NTPD program, whereas the University of Utah benefits by avoiding the high startup and maintenance costs of repackaging their curriculum into a distance learning format. Utah pharmacists also benefit from the agreement by having access to ISU's NTPD program at a reduced tuition rate. As the pool of prospective NTPD program applicants dries up, many more universities may consider such collaborations to minimize costs, while still providing this essential educational service to practitioners.

Considerable resources have been allocated toward the development and implementation of NTPD programs, generally without any corresponding increase in appropriated budgets or overall institutional support. Hence, programs have been largely developed and are solely dependent on practitioner-derived tuition fees to maintain and support their existence. Total tuition costs for in-state residents of NTPD programs range from approximately $5000 to $15,000, excluding the costs of textbooks, computer use, etc. Nonresident tuition rates are usually 2–3 times higher.

Financial cost, unfortunately, is a major impediment to participation. Because these programs are designed for full-time working practitioners, demonstration of financial need is usually difficult and most practitioner-students will not qualify for federal financial aid programs. Thus, for those individuals who do not work for institutions or corporations that offer employee educational benefits, financing their return to school will require careful consideration. Even with financial assistance, a substantial burden of the cost will accrue to the individual. Although a few programs may offer scholarship assistance specifically for nontraditional students, these are extremely rare.

Clearly established goals, strong self-discipline, and an extremely supportive family and employer are essential attributes of successful nontraditional students. Although schools/colleges have expended significant efforts to design and implement user-friendly programs to allow full-time practitioners to return to school, prospective candidates must approach this process with the same intensity and rigor expected of other doctoral-level programs. Thus, the goal of nontraditional education is not to make it easy to obtain the degree, but rather to make it easier to return to school. Substantial time, effort, and self-sacrifice can be expected of nearly all programs, and these generally will directly correspond to enhancement of clinical skills and abilities. At this juncture, the evolution of NTPD programs has virtually assured that practitioners will be required to *earn their doctorate* and that grandfathering of the Pharm.D. degree will not occur.

Considerable effort has gone into designing NTPD programs that achieve the same educational endpoints as their on-campus entry-level counterparts. The use of standardized patients as an assessment method has been proposed as a mechanism to document parity between nontraditional and traditional tracks.[26] Evidence supports the equivalency of nontraditional education;[24] yet, the issue is still somewhat controversial.[11] Hopefully, this will quickly disappear since NTPD programs are now required to demonstrate equivalent educational outcomes as part of their ACPE accreditation process.[27]

Perhaps more controversial is the relative quality and equivalency between various NTPD programs, especially with respect to major differences in clerkship requirements for some programs. The ability to take time off from work to complete full-time or even half-time clerkship experiences is certainly a major impediment to pursuing a NTPD, and flexibility in designing the clerkship program is imperative. This has resulted in development of truly unique experiential components in an attempt to overcome this critical element. The major issue is whether NTPD programs requiring primarily self-directed clerkships (i.e., no or very limited onsite preceptor supervision) are able to provide the breadth and depth of clinical educational experiences compared to with more traditional clerkship programs (i.e., student-practitioner progress directly monitored by onsite preceptor). Given the significant differences, debate will likely continue until more extensive experience accumulates or an objective comparison of NTPD programs and/or graduates can be made.

CONCLUSION

Final resolution and adoption of the Pharm.D. as the sole entry degree have provided the impetus for development of innovative nontraditional programs. Practitioners are now afforded a variety of equivalency-based academic degree programs from which to select. Consideration of career goals must be carefully weighed against the potential financial and personal costs.

ACKNOWLEDGMENT

The authors acknowledge Ms. Kathleen Moe for her assistance in collecting the individual NTPD program information.

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Nutraceuticals and Functional Foods

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INTRODUCTION

Functional foods and nutraceuticals are assuming a middle ground between food and drugs due to a growing body of evidence that supports their role in maintaining health and contributing to the treatment of diseases. Since Hippocrates advised "Let food be thy medicine and medicine be thy food," we have defined medicines and foods based on what is known about each substance in terms of efficacy, safety, and the significance of its perceived contribution to health. Over time, we tend to redefine these substances as our experience and expectations change. The ancient Greeks, for example, looked upon garlic as a performance-enhancing drug and officially sanctioned it for this use during the first Olympic games. During the age of sailing ships, lemons were dispensed to sailors to prevent and treat scurvy. John Woodall, the father of naval hygiene and a "Master in Chirurgerie," published "The Surgeon's Mate" in 1636, in which he wrote, "The juyce of lemmons is a precious medicine .... It is to be taken each morning two or three teaspoonfuls, and fast after it two hours."

Modern functional foods became available in the 1920s, when iodine was added to salt to prevent goiter. This was followed by vitamin D milk. Today, many Americans start their day with calcium-fortified orange juice (to strengthen their bones). Then, they spread a margarine that lowers cholesterol on folate-enriched toast (to protect their hearts and prevent birth defects).

DISTINGUISHING BETWEEN FUNCTIONAL FOODS AND NUTRACEUTICALS

It is not surprising that the terminology to define and promote these products is escalating (Table 1). For practical purposes however, two terms (*functional food* and *nutraceutical*) can be used to distinguish among nutritional products that make health claims beyond basic nutrition.

Functional foods, as defined by the American Dietetic Association, are products whose nutritional value is enhanced by the addition of natural ingredients. Functional foods may provide specific health benefits beyond basic nutrition when consumed as part of a varied diet.

Nutraceuticals, according to the American Nutraceutical Association, are functional foods with potentially disease-preventing and health-promoting properties. They also include naturally occurring dietary substances in pharmaceutical dosage forms. Thus, they include "dietary supplements" as defined by the Dietary Supplement Health and Education Act of 1994 (DSHEA).

From the FDA regulatory perspective, all substances that influence our health can be divided into two groups: food and drugs, with food further divided into conventional food and dietary supplements (Fig. 1). Despite the fact that many terms are used to describe nutritional substances that influence health, each of these terms fits into one of these categories. When viewed in this way, healthcare professionals will be less susceptible to the vague claims that tend to characterize this growing field.[1]

EXAMPLES OF FUNCTIONAL FOODS

All foods are functional; however, the term *functional* refers to an additional physiological benefit beyond meeting basic nutritional needs (Table 2). For example, epidemiological data tend to show that cancer risk in people consuming diets high in fruits and vegetables is about one-half that seen among people consuming few of these foods.[2] Certain components from animal sources make similar contributions to health, including omega-3 fatty acids found in fish, calcium in dairy products, and the anticarcinogenic fatty acid known as conjugated linoleic acid in beef.[3]

Once the benefits of a key component in food are documented, the challenge is to increase its concentration, and presumably its benefits, while maintaining safety. For example, isoflavones in soy are phytoestrogens with a chemical structure similar to estrogen. Isoflavones may reduce cholesterol, but what is the risk of increasing the intake of a compound that may modulate estrogens? Knowledge of the toxicity of functional food components is crucial to improve their benefit–risk ratio. The efforts

DOI: 10.1081/E-ECP 120006312

Table 1 Categories of healthful foods and dietary supplements

Category/example	Description
Dietary supplements Products containing one of more of the following: • Vitamin, mineral, herb or other botanical • An amino acid or metabolite • An extract • Any combination of the above	• Products (other than tobacco) intended to supplement the diet. • May be marketed in a food form if not "represented" as a conventional food and labeled as a dietary supplement. • Specific health or structure/function claims[a] can be made if the FDA deems adequate scientific substantiation exists.
Fortified foods • Breakfast cereal • Vitamin B added to baked goods	• Foods enriched with vitamins and minerals, usually up to 100% of the DRI. • Often mandated by law to replace nutrients lost during processing.
Functional foods • Soy • Salad dressing with omega-3 polyunsaturated fatty acids • Carrots with 170% of daily requirement of vitamin A	• A food or ingredient that may provide a health benefit beyond the "traditional nutrients" it contains.[b] • Specific health or structure/function claims can be made if the FDA deems adequate scientific substantiation exists. • Super fortified foods have more than 100% of the DRI and/or foods with added botanicals or other supplements.
Medicinal foods • Food to treat diabetes, obesity, or heart disease, sold through physicians, not by conventional retailers	• Food formulated to be consumed or administered internally while under the supervision of a physician. • Intended for specific dietary management of a disease or condition for which distinctive nutritional requirements are established.
Nutraceuticals • Orange juice with calcium • Dietary/herbal substances in pharmaceutical dosage forms	• Dietary supplements and fortified foods enriched with nutrients not natural to the food.

DRI=dietary reference intake.
[a]Structure/function claims state that a product may affect the structure or function of the body (e.g., calcium builds strong bones, antioxidants maintain cell integrity, fiber maintains bowel regularity), but may not claim that a therapy can prevent or cure a disease (e.g., alleviates constipation).
[b]"Traditional nutrients" refers to vitamins and minerals considered essential to the diet and/or to correct a classical nutritional deficiency disease. For example, foods containing vitamin C to correct scurvy or vitamin D to alleviate rickets are not functional foods. However, soy, which contains soy protein and is associated with a reduced cardiovascular risk, is a functional food.
(From Ref. [8].)

that go in to making these determinations are costly. As a result, companies that are successful can be expected to market products that will be branded and extensively promoted (Table 3).

CHALLENGES FACING NUTRACEUTICALS

Some of the most popular nutraceutical products marketed today are botanicals such as St. John's wort, echinacea, ginkgo biloba, saw palmetto, and ginseng. Unfortunately, manufacturers are not required to prove their safety or efficacy before marketing them. Dosages are not standardized. The quality of the raw source and the plant parts used are not regulated. And, unlike prescription drugs or over-the-counter medicines, there is no federal quality control standard to ensure that the label reflects what is in the bottle.

The problem is illustrated by reports that labeled concentrations of active ingredients often significantly overestimate the content in the dosage form. In one report, nearly one-third of the brands tested did not contain what their manufacturers claimed.[4] It is a serous problem that undermines the nutraceutical market, encourages skeptics who criticize the value and role of nutraceuticals, and (most importantly) is potentially harmful to the public.

SIGNIFICANCE FOR PHARMACISTS

The issues surrounding nutraceuticals and functional foods are important to pharmacists for two reasons. It is

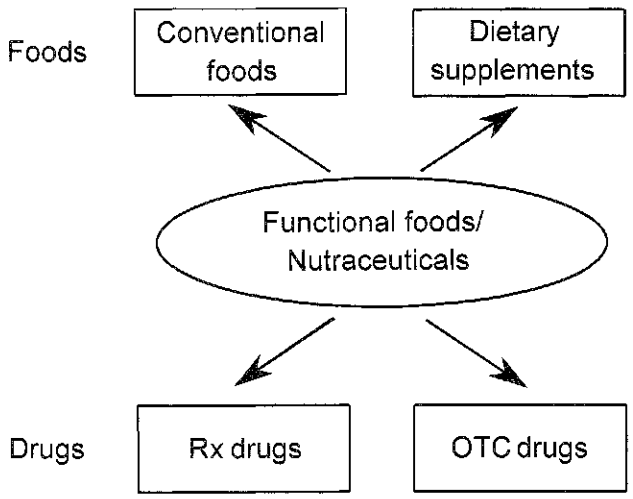

Fig. 1 Options for categorizing functional foods and nutraceuticals.

important to their patients and is certain to be the source of questions. Also, the growing field of nutraceuticals and functional foods is likely to change the practice of pharmacy over the next decade.

More than 100 million Americans regularly use dietary supplements, and in the year 2000, consumers spent about $16 billion on them.[5] Furthermore, 39% of Americans say they have made dietary changes to reduce their risk of getting cancer, 43% claim to take a daily multivitamin for cancer protection, while 21% take another form of nutritional or dietary supplement (i.e., concentrated doses of single vitamins, minerals, or herbal substances) to lower their cancer risk.[6]

Americans are concerned about their health and they view their pharmacist as an important resource for health matters. Almost two-thirds of respondents in one sample stated that they regularly talk with their pharmacist when choosing an OTC product, and 58% have come to think of their local pharmacist in the same terms as their family doctor.[6]

In the future, according to Dr. Benadette Marriott, who is vice president of programs and communications at the Burroughs Wellcome Fund, the need to guide consumers through the maze of functional foods and nutraceuticals may lead to significant changes in pharmacy practice. Food stores will continue to evolve into "one-stop wellness centers," where consumers go for basic wellness screening activities, nutritional counseling, and medication advice. At the center will be the pharmacy, where pharmacists will work with nutritionists and others to help consumers recognize their options and select among several sources of an ingredient in order to safely treat or lower their risk for disease.[1]

CASE HISTORY: YEAR 2010

Mr. D is a 50-year-old man with a family history of prostate cancer and a personal history that is remarkable for a diet high in saturated fats. He comes to the pharmacy knowing that his family and dietary history place him at risk. He has no symptoms or laboratory values consistent with prostate cancer but is committed to making changes in his life that will lower his risk. Part of his strategy includes eating more tomatoes to increase his intake of the antioxidant lycopene. However, he is confused because of a news story in which researchers reported that lycopene administered to mice as a supplement acted as a pro-oxidant and encouraged tumor growth.[7]

In addition to wanting to take an effective source of lycopene, Mr. D wants to know which is safest and most

Table 2 Examples of functional foods, their key components, and potential health benefits

Functional food	Key component	Potential health benefits
Black and green tea	Catechins	Reduce risk for cancer
Broccoli and other cruciferous vegetables	Sulforaphane	Reduce risk for cancer
Citrus fruits	Limonoids	Reduce risk for cancer
Fish	Omega-3 fatty acids	Reduce risk for heart disease
Fruits and vegetables	Many different phytochemicals	Reduce risk for cancer and heart disease
Garlic	Sulfur compounds	Reduce risk for cancer and heart disease
Oats and oat-containing foods	Soluble fiber beta glucan	Reduce cholesterol
Purple grape juice and red wine	Polyphenolic compounds	Support normal, healthy cardiovascular function
Soy foods	Soy protein	Reduce cholesterol
Tomatoes and tomato products	Lycopene	Reduce risk for cancer
Yogurt and fermented dairy products	Probiotics	Improve gastrointestinal health

Table 3 Examples of products marketed or planned to be marketed as functional foods by pharmaceutical companies

Novartis: Aviva product line	• Breakfast bars, cereals, and beverages. • Claims: Benefits the heart, bones, and digestion. • Marketed in United Kingdom and Switzerland. • U.S. launch planned.
McNeil Consumer Health, Division of Johnson & Johnson	• Benecol brand margarine, salad dressing, and health bars in U.S. • Claim: Reduce LDL cholesterol up to 14% within two weeks of product use. • In first few months, Benecol margarine captured ~2% of U.S. margarine sales.
Mead Johnson, Division of Bristol-Myers Squibb	• EnfaGrow nutrient-enriched oatmeal and snack line for toddlers, marketed primarily to physicians. • Allergy alert: EnfaGrow Nutritional Oatmeal for Toddlers in maple brown sugar and cinnamon and strawberry flavors may contain trace amounts of milk protein, not listed in the ingredients.[a] • Viactiv Soft Calcium Chews sold in U.S. grocery and drug stores. • Claim: To meet women's special nutritional needs.

[a]From Ref. [9].

economical. In the year 2010, there are no fewer than five sources of lycopene, listed here in order of increasing cost:

- Nutritional lycopene: vine-ripened tomatoes (and other foods).
- Organically grown sources of lycopene: organically grown tomatoes.
- Lycopene-enhanced functional foods: genetically enhanced tomatoes with guaranteed high levels of lycopene.[a]
- Nutraceuticals: dietary supplements that isolate and contain high levels of lycopene.
- Prescription drugs: pharmaceutical-grade lycopene containing the highest concentrations of lycopene and clinically tested to meet FDA standards for safety and efficacy.*

GUIDELINES

The challenge facing the pharmacist is to guide this patient through the maze of study results and conflicting claims. There are few absolute answers, but there are guidelines that can help consumers make intelligent decisions.[7] And it is likely that the guidelines for today will be valid a decade from now.

* Currently, not marketed.

Regard advertising and articles about supplements with caution:

- Be cautious of any product that claims to "boost" the immune system or "rejuvenate" health. Advise consumers to look for specific findings, not vague claims.
- Nutraceuticals can have side effects under certain circumstances and should be thoroughly tested before being used by the public.
- Remember, if it doesn't have side effects, it probably hasn't been thoroughly tested.

Natural first, supplement second:

- When there is a choice between a vegetable and a pill, recommend to eat the vegetable.
- Nutraceuticals are products that isolate recognized active ingredients. It is often not clear whether the active ingredient is as effective when taken in the absence of other nutrients found in food.
- When taking supplements, consumers should take them with food to aid absorption and minimize the risk of GI upset.

Read the label; then, get a second opinion:

- Before buying anything, read the label.
- Confirm the value of the supplement with a health care advisor.

Moderation is best:

- More is not always better; vitamin C, selenium, and vitamin D are examples where too little has no effect, but too much has adverse effects.

- Start with low doses and work up. A commitment to taking nutraceuticals is a long-term strategy. Starting doses that are too high increase the risk of side effects, which will dampen the consumer's resolve to continue treatment.

Keep everything in perspective:

- Supplements are only part of the picture. They are not substitutes for a healthy diet, stress reduction, exercise, weight control, and (when needed) prescription drug therapy.
- Nutraceuticals do not offset the negative effects of smoking.

Finally, remind consumers not to become obsessed by one disease. For example, men concerned about prostate cancer and women concerned about breast cancer should not ignore their risk factors for heart disease.

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DISTINGUISHED PERSONALITIES

Oddis, Joseph A.

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INTRODUCTION

Joseph A. Oddis served as the Executive Vice-President of the American Society of Health-System Pharmacists (ASHP, formerly the American Society of Hospital Pharmacists) for 37 years (1960–1997). During that period ASHP emerged as pharmacy's strongest membership association, with 31,000 members, a staff of 180, an annual budget of $30 million, and net assets of $30 million. Oddis's leadership was a major force behind establishing pharmacy as a clinical profession, establishing ASHP as the accrediting body for pharmacy residency and technician-training programs, organizing the world's largest, ongoing meeting of pharmacists (the ASHP Midyear Clinical Meeting), and creating the ASHP Research and Education Foundation. Oddis was also seminal to the publication of a periodical devoted to clinical practice (*Clinical Pharmacy*), as well as books considered essential to pharmacy practice (e.g., *The Handbook on Injectable Drugs*), and patient-oriented sources of drug information (e.g., *Consumer Drug Digest*).

EDUCATION AND TRAINING

Oddis graduated from Duquesne University in 1950 with a degree in pharmacy. He served as a staff pharmacist at Pittsburgh's Mercy Hospital before serving in the U.S. Army. He returned to Mercy Hospital as assistant director of pharmacy and later served as chief pharmacist at Western Pennsylvania Hospital. In recognition of his leadership, Oddis received five honorary doctor of science degrees: from the Massachusetts College of Pharmacy and the Philadelphia College of Pharmacy and Science in 1975, the Albany College of Pharmacy in 1976, Duquesne University in 1989, and Mercer University in 1995. He received an honorary doctor of humane letters degree from Long Island University in 1991.

MAJOR POSITIONS AND PROFESSIONAL INVOLVEMENT

In 1956 Oddis joined the American Hospital Association (AHA) in Chicago as the staff representative for hospital pharmacy. In 1960 he was recruited by ASHP and the American Pharmaceutical Association (APhA) as secretary of ASHP and director of the Division of Hospital Pharmacy at APhA. When the APhA position was dissolved a few years later, Oddis became full-time chief executive officer at ASHP, a position he held until his retirement in 1997.

For the International Pharmaceutical Federation (FIP), Oddis served as President, Section on Hospital Pharmacy (1977–1982); FIP Vice-President (1984–1986); President (1986–1990), and immediate Past President (1990–1994).

For the American Association for the Advancement of Science, Oddis was a Fellow; Secretary, Pharmaceutical Scientists Section (1968–1970); and Vice President and Chairman, Section on Pharmacy (1961).

For the American Society of Association Executives Foundation, Oddis was a member of the Board of Directors (1977–1978); Treasurer (1982–1983); Chairman (1984–1985), and immediate Past Chairman (1985–1986.)

ACCOMPLISHMENTS

Oddis's leadership at ASHP yielded a long list of achievements. The *American Journal of Health-System Pharmacy* (*AJHP*) grew from modest beginnings to the profession's most highly regarded peer-reviewed scientific journal. The *American Hospital Formulary Service* (*AFHS*) became a world-reknowned drug information system. Educational meetings grew in number, size, and quality; ASHP's Midyear Clinical Meeting became the largest meeting of pharmacists in the world. ASHP

DOI: 10.1081/E-ECP 120006256

created and published more than 100 practice standards, as well as numerous guidelines, technical assistance bulletins, and position papers, many of which dealt with clinical pharmacy issues. In 1962, ASHP produced the first Statement on Accreditation of Hospital Pharmacy Internship Training Programs; in the Oddis era more than 10,000 residents graduated from 375 programs accredited by ASHP. In 1968, ASHP created the ASHP Executive Residency Program, which produced 26 graduates under Oddis's stewardship. In 1969, the ASHP Research and Education Foundation was created. In addition to the numerous honorary doctor of science degrees bestowed on him, Oddis received the Harvey A.K. Whitney Lecture Award, pharmacy's highest award, presented by ASHP in 1970; the Hugo H. Schaefer Award, presented by APhA in 1983; the Donald E. Francke Medal, presented by ASHP in 1986; the Remington Honor Medal, presented by APhA in 1990; and the Andre Bedat Award, presented by FIP in 1994.

INFLUENCE ON CLINICAL PHARMACY PRACTICE

Oddis, more than any other pharmacy association executive, advanced the role of pharmacists in healthcare. He was a key facilitator and motivator in the 1960 creation of the ASHP/AHA joint statement of the legal basis of the hospital formulary system, widely regarded as a crucial catalyst for the development of clinical pharmacy services in hospitals. The quality and quantity of publications created by ASHP during the Oddis years stimulated pharmacy's development as a clinical profession. As the sole accrediting body for residency and technician-training programs, ASHP during the Oddis administration contributed substantially to the skill levels of clinical pharmacy practitioners. Oddis was one of the profession's strongest advocates for making the doctor of pharmacy degree the entry-level standard. As much as anything else, it was Oddis's persistence—behind the scenes, in a gentlemanly and nonconfrontational manner—that crystallized these achievements for pharmacy.

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PROFESSIONAL DEVELOPMENT

Oncology Specialty Pharmacy Practice

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INTRODUCTION

Oncology pharmacy specialists have been recognized for their expertise and fundamental role in cancer care programs for more than 30 years. Oncology specialty pharmacy practice requires a diverse group of knowledge and skills and the ability to apply these principles to highly patient-specific clinical situations. Skilled practitioners must possess knowledge of malignant processes and how they are treated optimally with antineoplastic agents and ancillary medications. In addition, a solid foundation of general pharmacotherapeutics is essential, since oncology patients may require integrated care plans to address concomitant nonmalignant diseases.

In the clinical setting, the oncology specialty pharmacist is responsible for reviewing medication orders to ensure completeness and accuracy, and to minimize drug-related adverse effects; he/she also serves as a resource for drug and patient education information. Clinical practitioners actively participate in prospective therapeutic decision-making processes for treatment of individual patients with malignancy and serve as integral members of team efforts to evaluate and identify specific agents, clinical indications, and treatment regimens for their use within a healthcare system. Although the types of settings in which oncology pharmacy specialists practice may be quite different, their clinical practice roles share a common set of knowledge, skills, and responsibilities.

CLINICAL PHARMACY OPPORTUNITIES

Clinical pharmacy opportunities for oncology pharmacy specialty practitioners are available in every type of pharmacy practice setting including patient care, research, the pharmaceutical industry, medical communications, and governmental agencies (Table 1). Direct patient care settings include adult, pediatric, and specialty oncology practices; palliative care and hospicare; and home care patient care services. Since the majority of oncology patient care is conducted in outpatient clinics, tremendous practice opportunities exist in these typically busy care settings. In addition, the growth of stem cell transfusion protocols has led to wider use of these often-complex and toxic treatment programs, leading to increased need for specialty practitioners to work with oncology transplant services.

Several factors have driven the demand for oncology pharmacist involvement in patient care, including disease-management diagnosis-related group (DRG) reimbursement policies, high-cost oncology drugs, increasing complex technology, high risk for medication errors, the need for outcomes-based research, and public and health professional concerns regarding patient safety.[1] The type and extent of pharmacists' responsibilities are influenced by institutional needs and the individual pharmacist's professional strengths and training. The focus of one's professional responsibilities may also change over time. It is therefore important to recognize that, for most practitioners, no single clinical practice model represents the entire scope of their professional activities during their career.

Pharmacists who practice in oncology patient care settings are responsible for reviewing medication orders, monitoring patients' therapies, and providing drug information to patients and healthcare providers. In an early survey of pharmacists who were members of the American Society of Health-System Pharmacists (ASHP) Oncology Special Interest Group (SIG), the bulk of practice activities described include patient-oriented services (performing medication histories and medication discharge counseling), drug distributive activities (determining appropriate volumes and diluents for admixture solutions and dispensing medications), participating in drug studies as a clinical investigator, providing in-service education programs, assuming management responsibilities (determining pharmacy budget appropriations, performing inventory maintenance and management, and assuming managerial responsibilities for pharmacy personnel), and providing therapeutics consultations.[2] Regardless of whether the pharmacist is directly responsible for dispensing or overseeing the release of medications for patients, medication order review is a fundamental responsibility shared by all clinical oncology

Table 1 Oncology specialty practice roles

- Oversee cancer drug preparation and dispensing in patient care settings
- Direct patient care
- Investigational drug services
- Research
- Drug information
- Educational instruction
- Outcomes assessment
- Pharmaceutical industry
- Medical communications

pharmacists. Preventing medication errors is a vital goal of this process.

Medication Order Review

Oncology pharmacists are responsible for ensuring that medication orders for antineoplastic agents that are released for patient care administration are complete, accurate, and appropriate for each patient. The increased use of cytotoxic agents for patients with nonmalignant diseases, such as rheumatologic and dermatologic disorders, has led to more complex therapies in patient care settings where healthcare professionals are less familiar with these agents and their potential toxicities. While nonspecialists assume this role in many settings, institutions that provide care to large numbers of patients with cancer most often involve pharmacists with specialty training in oncology to minimize medication errors and optimize pharmacotherapy.

Strategies for preventing medication errors in oncology include using of standardized chemotherapy order forms, conducting computer-assisted chemotherapy order screening, allowing only pharmacists to prepare cytotoxic agents, and double-checking drug orders.[1] Several organizations have developed processes for uniform medication order reviews; in addition, institution-specific processes may be developed through the pharmacy and therapeutics and other interdisciplinary committees. Although a number of computerized medication order-screening software programs are increasingly utilized, the flagging of excessive drug doses is not the only basis for order review. Also, if the patient has received prior courses of chemotherapy, a comparison between the new and past orders should be made; significant discrepancies are addressed with the prescriber.

Key recommendations for preventing chemotherapy medication errors are well recognized and include: education of healthcare providers, an established dose-verification process, established dose limits, use of standardized prescribing vocabulary, patient education, interdisciplinary team review of medication errors and communication issues, and medication error reporting with cooperation from drug manufacturers.[3] The use of standardized chemotherapy order forms improves completeness of physician ordering, prevents potential medication errors, and reduces the time spent by pharmacists clarifying orders.[4] The oncology pharmacist is instrumental in the development of such forms. Chemotherapy checklists can also be used in the drug order verification process. Some institutions include these on the product patient label, as well.

In an effort to identify opportunities to reduce chemotherapy medication errors, a multidisciplinary committee reviewed practices of more than 100 hospitals' processes to prevent chemotherapy errors.[5] A summary of the authors' recommendations is presented in Table 2. The nurse and pharmacist should both be independently responsible for checking each item.

Drug Handling, Preparation, and Dispensing

Pharmacists assume overall responsibility for the acquisition, preparation, handling, and distribution of antineoplastic agents within their healthcare system. Pharmacists are necessary to ensure optimal safety and minimal expo-

Table 2 Recommendations for chemotherapy order verification

- Check entire set of chemotherapy orders against an acceptable reference.
- Verify current body surface area, height, and weight.
- Verify the final dose of each drug.
- Check the rate of administration, amount, and type of admixture solution.
- Check the antiemetic regimen and prehydration and posthydration orders for omissions and additions of ancillary medications.
- Compare current chemotherapy orders with previous orders and discuss significant discrepancies with prescriber.
- Check that an x-ray has been performed and read to confirm central venous access for newly placed lines for vesicant chemotherapy infusions.
- Confirm parameters with standard references or the research protocol to determine that any dose modifications that have been made are appropriate; discuss significant discrepancies with prescriber.
- Determine that pertinent (hematologic, organ-specific tests based on the chemotherapeutic agents used) laboratory values are within normal parameters; discuss significant abnormalities with prescriber.

(Adapted from Ref. [5].)

sure risks for themselves, other pharmacy staff, individuals who administer cytotoxic drugs, and patients who receive those agents. Although clinically focused practice positions typically do not require pharmacists themselves to prepare antineoplastic agents, in many settings, those activities often comprise part of their responsibilities. Regardless of whether those pharmacists actually prepare the agents themselves, the overall responsibility for drug handling, preparation, and appropriate dispensing falls to the pharmacist. He or she is typically involved in developing training, recertification, and employee-monitoring policies. Determining technician competencies for drug preparation and handling and documenting technician training are also important components of this process.[6] Anyone who is involved with any aspect of this process needs to understand the risks and protective measures that are available to them. The Occupational Safety and Health Administration (OSHA) Technical Manual on Hazardous Drug Exposure[41] and the ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs[42] are easily accessible resources. The ASHP Technical Assistance Bulletin,[7] last reviewed in 1996, is currently under review and updated guidelines will likely be released in the near future. Criteria for facilities and personnel for administration of parenteral antineoplastic agents have been developed by the American Society of Clinical Oncology.[8]

Drug Administration Policies and Guidelines

Oncology pharmacy specialists provide guidance and assistance to address drug administration issues and provide input toward the development of guidelines for administration of certain medications within their healthcare system. The rationale for such guidelines may involve the potential to reduce medication errors, infusion-related reactions, or treatment-related toxicities or to optimize drug delivery of time-consuming treatment regimens in busy outpatient treatment settings. Oncology pharmacists, through their efforts in reviewing primary literature and participating as investigators in clinical studies, facilitated the recognition that certain agents that were initially approved by the FDA for administration over 24 hours (i.e., pamidronate, paclitaxel) could be safely administered over shorter time periods.

Patient Education

Patient education is standard practice and crucial for patient well-being and compliance. As such, patients are typically required to provide written informed consent prior to receiving antineoplastic agents and other anti-cancer therapies. Pharmacists frequently collaborate with other healthcare practitioners to develop patient education materials to address general complications of their cancer treatment as well as drug-specific information sheets. Cancer.gov, a National Cancer Institute Web site for current and accurate cancer information, makes some of these materials accessible online.[43] Chemotherapy and You: A Guide to Self-Help During Treatment, a patient-focused booklet that addresses common treatment-related side effects and coping strategies, is also available online.[44] Many commercially available print and online drug information resources provide patient cancer medication education sheets; however, practitioners often develop their own patient education information materials for use in their specific patient care settings.

Patient Monitoring

Patient monitoring functions comprise a key component of clinical pharmacists' activities in oncology practice. Examples of common patient care problems addressed by clinical oncology pharmacists are listed in Table 3. Based on their understanding of the nature and time course of specific drug-related toxicities and an individual patient's characteristics, pharmacists may anticipate certain treatment toxicities and provide input in the design of the regimen to minimize adverse outcomes. Drug dose reductions and use of hematopoietic growth factors, chemoprotective agents, certain antiemetic agents, or other ancillary medications may be recommended. For patients who develop significant toxic effects, pharmacists assess their current and previous drug therapy history to assist in managing these problems.

Table 3 Common patient care problems in oncology pharmacy practice

- Medication education and compliance
- Dose verification
- Adverse drug effects
- Nausea
- Mucositis
- Cytopenias
- Infection
- Fatigue
- Pain
- Nutrition
- Therapeutic drug monitoring
- Practice guideline development and adherence
- Medication error prevention and tracking
- Quality improvement
- Pharmacoeconomic assessment

Therapeutic drug monitoring is another important aspect of pharmacists' patient-monitoring responsibilities. Target blood concentrations of cyclosporin have been established for minimizing graft versus host disease and renal dysfunction whereas optimal busulfan blood concentrations are associated with minimizing graft versus host disease and venous occlusive disease. Serum methotrexate level determinations are important for establishing appropriate leucovorin rescue treatment regimens. The pharmacist ensures that the levels are obtained at the appropriate time intervals and are processed in a timely manner. When patients are discharged prior to having completed methotrexate serum level monitoring, pharmacists may continue to estimate methotrexate levels to determine an appropriate dosing schedule and duration of leucovorin therapy. Research investigations of therapeutic drug monitoring offer further opportunities to improve patient care. At St. Jude Children's Research Hospital, investigations by oncology pharmacy specialists demonstrate that, by individualizing doses of certain chemotherapeutic agents based on drug elimination, survival rates can be increased for children with acute lymphocytic leukemia (ALL).[9]

Therapeutic drug monitoring and pharmacokinetic dosing adjustments are also important for nononcologic agents as well. Aminoglycosides, vancomycin, and anticonvulsant agents are frequently administered to oncology patients; the patients may be followed by an institutional pharmacokinetics service or by the oncology pharmacy specialist. In selected situations, requests for drug levels may be initiated for agents that are not routinely monitored in general clinical practice.

Drug Information

Clinical pharmacists in all practice settings routinely provide drug information to other healthcare providers; drug queries are particularly common in oncology practice due to the specialized nature of these agents and complex treatment regimens. The use of oncologic agents for non-FDA-approved indications is not uncommon and many patients receive drugs for an off-label indication. Pharmacists are responsible for ensuring that the literature supports such uses and that therapy is delivered safely in conjunction with other agents that the patient may be receiving.

When new agents become available for use within a healthcare system, the oncology pharmacy specialist is usually the individual responsible for providing drug information to the general pharmacy staff, nursing staff, house staff, and prescribers. The provision of this information can be disseminated through memorandums, newsletters, e-mail notices, chemotherapy administration guideline updates, and/or interactive in-services. Pharmacists who spend a significant portion of their day in patient care areas may find that their presence stimulates even more requests for drug information from other healthcare providers.

At the National Institutes of Health Clinical Center, oncology clinical pharmacists participate as members on the NCI Physician's Data Query online cancer information service supportive care and drug information panels and serve on the Board of Pharmaceutical Specialties Council on Oncology Pharmacy Practice.[10] These pharmacists, in conjunction with the NIH Division of Safety, developed the first recommendations for safe handling and disposal of antineoplastic drug products and waste.

Education

Providing education to healthcare providers and trainees, in addition to patients, is an important responsibility of clinical practitioners. The interdisciplinary nature of oncology patient care practice settings makes them desirable experiential training rotations for medical, nursing, pharmacy, physician's assistant, social work, physical therapy, occupational therapy, and psychology students. Oncology clinical pharmacists likely interact with most of these disciplines in their practice setting and serve as primary preceptors for pharmacy students, residents, and/or fellows during their training program. Salary support for many practitioners is, in part, based on their responsibilities for pharmacy student education.

Cancer centers typically require nursing staff who administer cytotoxic agents to participate in chemotherapy certification programs. The oncology pharmacy specialist, in conjunction with oncology nurse specialists, generally participates in the administration of these programs. Pharmacists also participate in ongoing education programs for house staff and medical hematology-oncology fellows.

MODEL CLINICAL PRACTICES

It is not unusual that an individual patient, during the course of treatment for his or her malignancy, will receive care in both an outpatient and inpatient environment. Although most chemotherapy is administered to patients in ambulatory treatment clinics, some patients will be hospitalized to receive certain complex treatment regimens or for complications due to the treatments or underlying disease process. Those patients who are undergoing induction treatment regimens for an acute leukemia, re-

ceiving high-dose chemotherapy in preparation for stem cell transplantation, or receiving salvage treatment regimens for refractory tumors are most likely to be hospitalized sometime during the course of their disease. Due to the nature of patient problems and heavy practice workloads, busy cancer treatment programs require multiple clinical practitioners to cover ambulatory and inpatient care settings. Regardless of whether the patient care setting is inpatient or outpatient, the basic functions of the medication review and patient monitoring processes, as well as provision of drug information and patient education by oncology pharmacy specialists, are similar.

Inpatient Care Practice Roles

Typically, pharmacists attend and participate in patient care rounds and discussions with the medical staff. Even a small portion of time devoted to this activity can yield tremendous information that can provide the pharmacist with an opportunity to discuss intended therapeutic interventions or suggest modification or discontinuation of current therapies. This can improve the efficiency of the therapeutic decision-making process through facilitating immediate interventions and decrease unnecessary drug wastage by previewing medication orders before they are delivered to and prepared by the pharmacy. Examples may include initiating appropriate patient-specific antibiotic dosage regimens, ensuring appropriate first-line antiemetic prophylaxis, or recommending changes in analgesic therapy. In addition, the presence of the pharmacist in this setting generally stimulates questions by the medical staff, thereby providing opportunity to improve drug knowledge. Moreover, pharmacists may be alerted to certain patient-specific issues that may not be obvious through a review only of hospital orders or the patient's medical chart.

At the University of California, San Francisco, approximately seven clinical pharmacists provide oncology services to adult inpatients.[1] These practitioners perform admission medical histories, attend rounds with medical house staff, attend bone marrow transplant rounds, make therapeutic interventions, provide drug information to staff and patients, perform medication order reviews, perform ongoing drug utilization reviews and evaluation, follow practitioner adherence to institutional drug therapy guidelines, and coordinate medication discharge planning and counseling.

At Cedars-Sinai Medical Center, oncology pharmacists provide services to hospitalized patients on a specialized inpatient unit and in an ambulatory infusion center.[11] In these settings, targeted areas to improve patient outcomes, prevent adverse drug reactions, and reduce costs include the chemotherapy process (ordering, dispensing, and administration), treating patients with febrile neutropenia, and managing peripheral blood stem cell patients. A clinical pathway for treating febrile neutropenia, which includes the use of hematopoietic growth factors, was implemented and reevaluated. In patients undergoing peripheral blood stem cell transplantation, pharmacists screen medication orders and participate in patient care rounds to ensure that inappropriate medications are avoided, antiemetic therapy is safe and cost-effective, and electrolyte supplementation therapy is appropriate and well-tolerated.[11] Professional activities that are common in the inpatient treatment setting include pharmacotherapeutics monitoring, pharmacokinetic dosing, managing clinical protocols and critical pathways, maintaining patient profiles, conducting patient monitoring, and providing adverse drug reaction (ADR) reporting and documentation.

Depending on the institution, the nurses also attend patient care rounds with the medical staff or discuss patients' status with other healthcare professionals. Through these discussions, additional patient care issues are frequently identified. Discharge planning rounds typically involve social workers, patient representatives, and nurse case managers. The pharmacists may assist in this process by helping to initiate therapy that is appropriate for the discharge setting and that will be covered adequately financially. The knowledge that imminent discharge is pending may help the pharmacist to suggest converting parenteral drug therapy (e.g., antibiotics, analgesics, antiemetics) sooner during the hospitalization to get the patient stabilized on the new therapy prior to discharge. Pharmacists also assist in arranging for qualifying patients to enroll in indigent drug assistance programs. The Pharmaceutical Research and Manufacturers of America provides a directory of patient medication assistance programs.[45]

Inpatient cancer patient care settings differ among institutions. In some settings, patients are managed directly by internal medicine house staff; the oncologist may be an attending physician for that service or a hematology-oncology specialty service may interact with the medical house staff in a consultative arrangement. Patients may be admitted for direct care by a hematology-oncology specialty service or an oncology nurse practitioner service. Although patients' needs are the same, regardless of their primary care team, the pharmacists' interactions may vary, depending on those individuals. Furthermore, the pharmacists' position may be entirely based within the pharmacy department or supported by the hematology-oncology department. If the institution has a pharmacokinetics service, pharmacokinetics issues

Table 4 Specialty oncology patient care services

- Stem cell transplantation
- Pediatric oncology
- Gynecologic oncology
- Solid tumor services
- Surgical oncology
- Radiation oncology
- Palliative care
- Hematology
- Hospice
- Home infusion
- Outpatient clinics

may be addressed by that service or by the oncology pharmacist, or may be shared. The oncology pharmacist also interacts with other clinical pharmacists that are involved in a patient's care (e.g., infectious diseases, nutritional support, pain, etc.).

Institutions that care for large numbers of cancer patients also have subspecialty oncology services to which specific pharmacists may be assigned. Examples of these services are listed in Table 4. At M.D. Anderson Cancer Center, for example, clinical pharmacists provide direct patient care in concert with the leukemia, lymphoma, bone marrow transplantation, medical breast cancer, gastrointestinal, critical care, and pediatrics services. The clinical pharmacists participate in drug regimen design and monitoring; provide pharmacokinetic dosing recommendations, drug information, and comprehensive patient education; and precept experiential training rotations for residency candidates and pharmacy students.

Transitional Patient Care Practice Roles

In the transitional patient care setting, patients may be receiving follow-up from pharmacists for chemotherapy that has extended from the inpatient to the outpatient environment. Pharmacists may also expedite chemotherapy orders for patients who are being admitted.[1] An example of such a treatment setting where continuous pharmaceutical care is delivered is the autologous bone marrow transplant (ABMT) outpatient program at Duke University Medical Center.[12] This program required months of planning with input from nurses, physicians, and pharmacists to deliver pharmaceutical services to meet individual patients' needs. Patients undergo 5 days of hospitalization to receive high-dose chemotherapy, continuous hydration, and antiemetic therapy after which time they are discharged with hematopoietic growth factors, prophylactic oral antibiotics, antiemetics, and electrolyte supplements. Approximately half of patients require readmission to the inpatient unit during this period of care. Antibiotic use guidelines for prevention and management of infection were developed and a clinical pharmacist is responsible for following pharmacokinetic parameters, toxicities, and microbiologic results for all patients. A system was developed in which drugs could be supplied to patients in the clinics and drug usage could be tracked for patient profile records and reimbursement purposes. A bone marrow transplant clinical pharmacist is available on-call to answer questions and to meet with patients at the clinic site if necessary. Delivery of pharmacy services through the entire treatment program is achieved through coordination efforts between the bone marrow transplant clinical pharmacists, the outpatient pharmacy, and the inpatient pharmacy satellite and facilitates a cost-effective and safe approach to administering high-dose chemotherapy to patients with solid tumors.

In an evaluation of system distress in this treatment setting, the most frequent symptoms involved loss of appetite, fatigue, insomnia, and intermittent nausea.[13] Medication compliance was determined to be greater than 90% and is believed attributable in part to patient and caregiver education by pharmacy and nursing personnel.

Outpatient Care Practice Roles

Clinical practice opportunities for oncology pharmacy specialists in outpatient treatment settings are significant as patients continue to receive increasingly complex anticancer therapies outside of the inpatient unit. Pharmacists conduct medication and patient profile reviews, perform medication histories, provide patient counseling and drug information, and participate in therapeutic decision-making. Within Veterans Affairs Medical Centers and some other practice settings, pharmacists see patients as primary care providers and initiate prescriptions for analgesics, growth factors, antiemetics, and other ancillary medications by protocol. The scope of clinical pharmacy practitioners' activities in oncology clinics is not well documented in the literature, however.

Raehl et al. reviewed results of questionnaires that were sent to directors of pharmacy in one-half of acute-care general medical-surgical hospitals in the United States that had at least 50 licensed beds to determine the extent that pharmacists provide ambulatory clinical pharmacy services.[14] Overall, pharmacists performed non-dispensing activities in ambulatory clinics in 19% of responding hospitals. Pharmacist involvement in oncology clinics occurred in 9% of institutions, second only to diabetes clinics (10%), and was more common than in cardiology (6%) or geriatrics, infectious disease, or pain clinics (4%).

In a prospective study to evaluate the impact of a clinical pharmacist in outpatient hematology-oncology clinics, patient charts and profiles were reviewed and patient interviews were conducted to obtain medication histories.[15] Within a 36-day time period, 211 interventions were documented; the majority of these interventions were not related to chemotherapy. The most frequent activities consisted of patient counseling and therapeutic recommendations. Of the problems identified, most were of high and moderate significance and pharmacy interventions yielded positive clinical outcomes. The physician acceptance rate to pharmacists' interventions was 94.5%.

In a unique practice role at the University of California, San Francisco (UCSF), a clinical pharmacist has been responsible for setting up chemotherapy and heparin administration via external or implanted infusion pumps.[1] The pharmacist also monitors the patient for treatment toxicities and efficacy, and provides pump maintenance. Thus, this practice setting enables the pharmacist to manage patients' outpatient chemotherapy first-hand, identify potential treatment-related problems, and initiate any necessary changes to optimize the treatment regimen. In addition, UCSF has recently implemented a distribution and clinical pharmacy service 40 hours a week using 5 pharmacists (4 with specialized training in oncology). These pharmacists work out of the Cancer Infusion Center and service 60 to 70 patients weekly.

Oncology pharmacists who care for patients in outpatient practice settings typically review patients' medication and medical profiles in advance of seeing the patients. This enables them to identify those individuals who are most likely to have medication-related issues or poor symptom management, and who will benefit from the pharmacist's interventions.

Investigational Drug Use and Management

Investigational drug use is an important aspect of pharmacotherapy for patients with malignancies. Oncology pharmacy specialists have an important role throughout the investigational drug use process; their responsibilities may involve directly maintaining drug-dispensing records and investigational protocols, participating in protocol development, having membership on institutional review committees, developing and disseminating information about the protocols and drugs to the pharmacy and nursing staff, and coordinating protocol management between study investigators, institutional staff, and study sponsors. Protocols for the use of investigational agents are developed and made readily available to all involved personnel. Included in these protocols are drug-specific characteristics and information that would not otherwise be readily available from typical drug information resources. At many institutions, these activities comprise the sole responsibilities of one or more pharmacists dedicated to research protocols and investigational drugs. Cancer centers also often have a clinical trials review committee that is separate from the Human Subjects Review Board. Pharmacist participation in any initial trial review process is crucial to ensure that the project is feasible, coordination and dispensing practices are worked out, and any clinical trial involving chemotherapeutic agents does not have a significant negative financial impact on the institution.

Situations may arise when a patient is in need of a drug that is not available commercially or in an ongoing clinical trial at the institution. The oncology pharmacy specialist may arrange to obtain the drug which may only be available from the pharmaceutical company or the National Cancer Institute for nonresearch (compassionate) use.[16] The NCI Cancer Therapy Evaluation Program (CTEP) Treatment Referral Center provides guidelines and contact information for this process.[46]

Drug Information

While provision of drug information comprises a portion of an oncology pharmacy specialist's daily activities, some practitioners devote their entire career to the practice setting in drug information. Large comprehensive cancer centers such as Memorial Sloan-Kettering and M.D. Anderson are examples of institutions where care is devoted to patients with cancer and workload justifies having an oncology clinical pharmacy specialist in drug information. Pharmacists resolve general oncology drug-related queries and provide key information to solve a specific patient problem. However, their responsibilities extend beyond these activities.

Pharmacists serve as members of the healthcare system's Pharmacy and Therapeutics Committee which directs the review process for considering medication additions to and deletions from the drug formulary. The committee may review and manage data from the ADR reporting program and from medication usage evaluations and reviews, and may monitor policies for medication use guidelines.

Other institutional programs that typically involve pharmacists include pharmacoeconomics, outcomes research and management, quality improvement, and reimbursement assistance programs.

Clinical Research

Patient participation in clinical research trials is a significant component of cancer care therapy, particularly

at comprehensive cancer centers and their affiliated medical practices and institutions. Whereas all oncology pharmacy specialists facilitate these activities, some practitioners focus their entire clinical practice in clinical research. Examples of their responsibilities include developing and reviewing research and funding proposals, screening and recruiting patient participants, overseeing medication disbursement, evaluating patient response and treatment outcomes, managing adverse effects, providing patient education, overseeing study records and report forms, reviewing and interpreting study data, and summarizing and reporting study results.

Clinical pharmacists participate as principal and coinvestigators on studies that are purely clinical in nature, basic and translational research, pharmacoeconomic studies, and outcomes-based research. Oncology pharmacy specialists have had a significant impact on oncology therapeutics through their participation in trials in drug development (pharmacokinetics, pharmacodynamics, and pharmacogenetics), supportive care, pharmacoeconomics, and outcomes research. Several oncology pharmacy specialists receive NIH support for their research activities.

DOCUMENTED BENEFITS OF ONCOLOGY SPECIALTY PHARMACY PRACTICE

The benefits of oncology specialty pharmacist practitioners are evidenced by the high demand for skilled clinical practitioners in oncology patient care settings. Furthermore, the Board of Pharmaceutical Specialties (BPS) recognized oncology as a pharmaceutical specialty in 1996. Information regarding the specialty certification process can be accessed at the BPS Web site.[47] Pharmacists are examined on their ability to collect and interpret clinical data to recommend, design, implement, monitor, and modify pharmacotherapeutics plans and optimize drug use for patients with cancer; basic knowledge of malignant disease processes and their management; ability to provide education and medication-related counseling, and ability to address public health issues related to oncology pharmacy practice; and knowledge of the drug development process. The petition requesting specialty recognition of oncology pharmacy practice to the BPS in 1992 delineated the societal need and demand for highly skilled oncology pharmacy practitioners.[17]

Ignoffo and King have identified potentially important patient outcomes related to anticancer therapy[18] (Table 5). By documenting the incidence of specific outcomes associated with patient care services, pharmacists can establish a threshold at which corrective measures can be instituted. Quality-of-life issues related to cancer patient care are a particularly active area of investigation. Both disease and symptom-specific assessment tools are available and can be used to document quality-of-life outcomes for individual patients and within a treatment population.

Table 5 Outcomes related to anticancer therapy

Desirable outcomes	Undesirable outcomes
Cure	Mortality
Improved survival	Progression of disease
Decreased mortality rate	Worsening of symptoms
Slowing of disease progression	Side effects
Decreased symptoms	Severe organ toxicity
Prevention of disease symptoms	Increased cost of ancillary therapies
Decreased cost of treatment	
Low incidence of adverse effects	Drug resistance

(From Ref. [18].)

Although the impact of this has not been formally ascertained, a method for designing and implementing toxicity outcome indicators for specific chemotherapy protocols has been described.[19] For each clinical protocol, clinical monitoring criteria were established; pharmacists are able to use predetermined agent-specific monitoring and toxicity ratings to document and improve pharmaceutical care services for oncology patients.

Practice Guideline Development and Implementation

Oncology pharmacists develop drug and use practice guidelines; the impact of these guidelines has been reported extensively at professional meetings and to some degree in the professional literature. Hirsh et al. report that pharmacist involvement in the development and implementation of guidelines for managing extravasations from antineoplastic agents resulted in prompt and uniform management of these drug effects.[20] However, the magnitude of this impact was not quantified.

Pharmacists who have been responsible for the design and implementation of antiemetic dosing guidelines have resulted in significant cost savings at many institutions.[21,22] In addition, patients who are treated according to established practice guidelines have satisfactory or improved antiemetic control.[22,23] Moreover, institutional drug use guidelines serve as educational tools and help to improve the drug-ordering and -administration

process. Significant cost savings and improved health outcomes have resulted from practice guidelines for hematopoietic growth factors and intravenous-oral drug interchange programs.

Publications by NIH Clinical Center clinical oncology pharmacists have received national attention and improve pharmacy practice processes; examples include ways to standardize expression and nomenclature of cancer treatment regimens[24] and pharmacy procedures for dealing with gene therapy products.[25]

Through a pharmacist's development of a clinical pathway for a methotrexate infusion protocol in pediatric patients, prechemotherapy hydration parameters were reached sooner and length of stay decreased from an average of 3.27 days to 2.4 days.[26] This was associated with a savings of approximately $600 per patient. At the same institution, a change in empiric antibiotic therapy in penicillin-allergic patients and other changes resulted in a decrease in length of stay by approximately one day (average 5.48 days versus 4.66 days) that was associated with a savings of approximately $1500 in direct costs per patient. Criteria for developing, implementing, and evaluating critical pathways in oncology practice have been published.[27–29]

Oncology Pharmacy Specialist Interventions

McClennan et al. conducted a prospective 2-month intervention study to determine clinical outcomes associated with pharmacist interventions at a tertiary referral cancer institute in Australia.[30] Clinical pharmacists documented clinical interventions and relevant patient information which were assessed by an independent pharmacist. Members of the healthcare team reviewed and discussed medical progress notes to determine outcomes. Of 674 total interventions that were documented during the study, outcomes were assessed for 10% of the interventions reported; 90% of the interventions led to documented clinical benefit. Pharmacist interventions most frequently consisted of initiating changes in drug therapy associated with antiemetic, antimicrobial, and analgesic agents.

Pfeiffer documented the impact of an oncology pharmacist's review of chemotherapy administrations.[31] The pharmacist reviewed chemotherapy admissions on a monthly basis for 20 months. Pertinent patient demographic data, chemotherapy administrations information, and admissions stay data were collected and were compared to an ideal that was predetermined based on the institution's admissions standards and chemotherapy care maps. The pharmacist identified opportunities for education for cases where length of stay exceeded the institution's standards or where problems were identified following a discussion by the Oncology Care Committee. The pharmacist provided education in the form of in-services or written material to the appropriate staff, resulting in a reduction in the average length of stay for chemotherapy administration, the number of variances in timing of chemotherapy, and the number of problem cases.

An analysis of self-reported interventions by hematology-oncology pharmacists and staff was also performed to document pharmaceutical care interventions over a period of approximately 8 months at the Walter Reed Army Medical Center.[32] The interventions were analyzed to determine the types of interventions that are most frequently performed, prescribing errors encountered, medication cost avoidance that resulted from the interventions and types of interventions that are associated with medication cost interventions, and intervention acceptance rate by physicians. Interventions were entered into a personal computer and analyzed using CliniTrend Web Support System software (ASHP). Medication cost avoidance was determined if less medication was used, an equally effective but less costly medication was used, or a medication that could not be reused was not prepared.

A total of 503 interventions were reported; clinical consultations, correction of prescribing errors, and patient treatment procedures accounted for approximately two-thirds of the interventions (Table 6). In this study, all clinical interventions were related to chemotherapy-related toxicities or drug-dosing and -administration issues. The 167 documented clinical consultations were related to nausea or vomiting (29.3%), chemotherapy dosing or

Table 6 Summary of interventions reported by hematology-oncology pharmacists at Walter Reed Army Medical Center (October 1, 1995–May 31, 1996)

Intervention	Number	%
Clinical consultation	167	33.2
Correction of prescribing error	85	16.9
Patient treatment procedure	65	12.9
Clarifying/verifying prescription with physician	38	7.5
Other	33	6.6
Enrolling/monitoring patient in clinical trial	28	5.6
Formulary or therapeutic interchange	26	5.1
Compatibility consultation	23	4.6
Verifying patient's chemotherapy schedule	20	4.0
Drug information counseling for patient	10	2.0
Alerting physician of need for a test dose	5	1.0
Patient counseling (other than drug information)	3	0.6

(From Ref. [32].)

administration (22.7%), general clinical consultations (18.0%), hematologic toxicity (9.0%), pain control (7.8%), other toxicities (7.2%), and mucositis (3.0%), or were allergy-related (3.0%). The impact of these consultations on health outcomes was not determined but likely contributed to improve patient care. Physicians accepted 488 (97%) of the pharmacy-initiated interventions. The total medication cost avoidance was $23,091; $19,696 (85.3%) was associated with correction of prescribing errors.

At the Baltimore Cancer Research Center, an NCI cancer treatment unit located in a U.S. Public Service hospital, pharmacists demonstrated that their counseling interventions improved patient adherence to medications. After pharmacist counseling, the patient compliance rate to oral antibiotic medication regimens for gut sterilization increased to 90% compared to 65% before counseling. A subsequent discontinuation and reinstitution of pharmacist counseling resulted in changes in compliance rates back to 65% and 90% again, respectively.[10]

Reimbursement Assistance and Investigational Drug Services

Through pharmacist involvement with other healthcare providers, identifying opportunities for medication reimbursement from drug manufacturers with indigent drug access programs can result in significant cost savings. In a program for procuring medications at no cost for indigent patients, a full-time pharmacist was responsible for identifying qualifying patients, assisting in the application process, and coordinating receipt and distribution of the medications.[33] In 1992, during the first year of the program, 200 patients were served and the potential cost avoidance resulting from obtaining these free medications was estimated at $150,000. The medications obtained included immune globulin, antiemetics, growth factors, cancer chemotherapy, antimicrobials, and interferons.

Pharmacy-managed investigational drug services represent an additional opportunity to reduce costs, particularly in oncology patient care settings where there is high-volume use of investigational drugs. In a study of cost avoidance associated with investigational drug services at two institutions in Washington State, drug costs associated with acquired immunodeficiency syndrome and oncology accounted for the largest figures.[34]

Patient Care Services

Oncology pharmacist participation in home delivery of chemotherapy for selected patients with good home care support can result in cost savings with antiemetic control.[35] Pharmacist involvement with infusion pump use and patient education services for drug reconstitution and self-injection have resulted in reduced medical costs that were recognized more than 20 years ago.[36,37] At many centers where patients are treated using ambulatory drug infusions, pharmacists decide how the drug will be prepared for delivery based on patient factors, drug stability data, and what type of pump is available. The pharmacist may also determine what type of pump will be used, how often the patient will return to the infusion center for follow-up during the treatment, and whether the patient will change the medication bags at home. During the treatment period, the patient may return to the infusion center to see the pharmacist to have the pump refilled or checked, receive additional patient education, or undergo monitoring for drug toxicities; follow-up with the oncologist may not occur until the infusion has been completed.

RESOURCES FOR ONCOLOGY PHARMACY PRACTICTIONERS

Oncology Practice Information and Guidelines

Oncology pharmacy specialists frequently participate in developing and monitoring adherence to health system guidelines for patient care. Several professional organizations have developed guidelines which serve as valuable resources for practitioners (Table 7). Information and treatment guidelines for cancer pain management have been developed by the American Pain Society and the Agency for Healthcare Policy and Research (AHCPR). Furthermore, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO)[48] has developed standards for assessing and managing pain in accredited healthcare organizations. Standards are available for ambulatory care, behavioral healthcare, home care, healthcare network, hospital, long-term care, and long-term care pharmacy practice settings. Internet Web sites for pharmaceutical manufacturers of analgesics such as Roxane Laboratories[49] and Purdue Pharma L.P.[50] are also sources for professional and patient-oriented information and resources. Talaria is a cancer pain management resource for healthcare professionals that provides multimedia instructive and interactive tools regarding pain management, in addition to general technical information.[51] The National Comprehensive Center Network (NCCN), American Society of Clinical Oncology (ASCO), and the American Society of Health-System Pharmacists (ASHP) are among several groups that have produced practice guidelines for cancer or supportive care treatments.

Table 7 Resources for oncology practice guidelines

Organization	Web site URL	Applicable contents
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahcpr.gov/clinic/cpgonline.htm	Online clinical practice guideline for management of cancer pain. References include a clinical guide, quick-reference guide, and consumer version (English and Spanish language available). Note: This was published by the AHCPR in 1994 (Publication No. 94-0592: March 1994) and is recognized as being in need of revision.
American Cancer Society	http://www.cancer.org	Guidelines for breast and prostate cancer treatment (developed in conjunction with the National Comprehensive Cancer Network (NCCN); recommendations for the early detection of breast, prostate, colon and rectum, and uterine cancers.
American Pain Society	http://www.ampainsoc.org	Consensus and quality improvement guidelines for treatment of acute and chronic pain.
American Society of Clinical Oncology (ASCO)	http://www.asco.org	Clinical practice guidelines for chemotherapy and radiotherapy protectants, hematopoietic colony-stimulating factors, antiemetics, bisphosphonates in breast cancer, and treatment of selected neoplastic diseases.
American Society of Health-System Pharmacists	http://www.ashp.org	Guidelines for managing postoperative and chemotherapy- and radiation-therapy-induced nausea and vomiting.
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm	Online Cancer Management Manual with disease management guidelines.
Cancer Care Ontario Program in Evidence-Based Care and the Cancer Care Ontario Practice Guidelines Initiative	http://hiru.mcmaster.ca/ccopgi/index.html	Clinical practice treatment guidelines for numerous malignancies and use guidelines for supportive care agents.
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org	Approximately 17 cancer centers across the United States are members of this organization. The NCCN develops cancer screening, prevention, detection, treatment, and surveillance guidelines for numerous malignancies and supportive care therapies.
National Cancer Institute	http://ctep.cancer.gov/index.html	Gateway to National Cancer Institute information and resources for: cancer information, clinical trials, statistics, research programs, and research funding.
PDQ®–NCI's Comprehensive Cancer Database	http://www.cancer.gov/cancer_information/pdq/	Cancer information summaries, including screening and detection, prevention, treatment, genetics, and supportive care information.

Table 8 Resources for drug handling, drug development, and investigational drug management

American Society of Health-System Pharmacists	http://www.ashp.org/	ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs.
Cancer Therapy Evaluation Program (CTEP)	http://www.cancer.gov/clinical_trials/	Information for investigators, healthcare professionals, and patients related to cancer drug development and clinical trials; guideline and policy information for clinical trials and investigation drug use and accountability.
Cancer Trials Support Unit (CTSU) of the National Cancer Institute	http://cancertrials.nci.nih.gov	Investigator's Handbook for participants in clinical studies of investigational agents; directory of research tools and services for cancer researchers; clinical trials information; links to cooperative study group Web sites.

Table 9 Selected oncology-specific reference texts

- *Cancer Principles and Practice of Oncology*, 6th Ed.; DeVita, V.T.; Hellman, S.; Rosenberg, S.A., Eds.; Lippincott Williams and Wilkins: Philadelphia, 2000.
- *Cancer Chemotherapy and Biotherapy: Principles and Practice*, 3rd Ed.; Chabner, B.A.; Longo, D.L., Eds.; Lippincott Williams and Wilkins: Philadelphia, 2001.
- *Principles and Practice of Supportive Oncology*; Berger, A.M.; Portenoy, R.K.; Weissman, D.E., Eds.; Lippincott-Raven: Philadelphia, 1998.
- *The Chemotherapy Sourcebook*, 3rd Ed.; Perry, M.C., Ed.; Lippincott Williams and Wilkins: Philadelphia, 2001.
- *Cancer Chemotherapy Handbook*, 2nd Ed.; Dorr, R.T.; Von Hoff, D.D., Eds.; Appleton and Lange: East Norwalk, 1994.
- *A Clinician's Guide to Chemotherapy Pharmacokinetics and Pharmacodynamics*; Grochow, L.B.; Ames, M.M., Eds.; Williams and Wilkins: Baltimore, 1998.
- *Cancer Chemotherapy Pocket Guide*; Ignoffo, R.J; Viele, C.S.; Damon, L.E.; Venook, A., Eds.; Lippincott Williams and Wilkins: Philadelphia, 1997.
- *William's Hematology*, 6th Ed.; Beutler, E.; Lichtman, M.A.; Coller, B.S.; Kipps, T.J.; Seligsohn, U., Eds.; McGraw-Hill: New York, 2000.
- *Hematology: Basic Principles and Practice*, 3rd Ed.; Hoffman, R.; Benz, E.J.; Shattil, S.J.; Furie, B.; Cohen, H.J.; Silberstein, L.E.; McGlave, P., Eds.; Churchill Livingstone: New York, 1999.
- *Concepts in Oncology Therapeutics*, 2nd Ed.; Finley, R.S.; Balmer, C., Eds.; American Society of Health-System Pharmacists: Bethesda, 1998.
- *Clinical Oncology*. Abeloff, M.D.; Armitage, J.O.; Lichter, A.S., Eds.; Churchill Livingstone: New York, 2000.
- *Principles and Practice of the Biologic Therapy of Cancer*, 3rd Ed.; Rosenberg, S.A., Ed.; Lippincott Williams and Wilkins: Philadelphia, 2000.
- *Principles and Practice of Gynecologic Oncology*, 3rd Ed.; Hoskins, W.J., Ed.; Lippincott Williams and Wilkins: Philadelphia, 2000.

Oncology Practice Tools

The FDA Oncology Tools Web site[52] is a general access point for oncology treatment and drug information for healthcare professionals. The site contains links to information regarding approved oncology drugs with approved use indications; oncology drugs advisory committee meeting calendar; meeting transcripts; disease summaries; FDA policies and publications regarding cancer and clinical research; oncology reference tools (toxicity grading criteria, performance status scales, disease staging information, dose calculator, human fluid and calorie calculator); the cancer liaison program; cancer information for patients; and contact information for FDA review divisions that are responsible for oncology products.

Investigational Drug Development and Drug Use Procedures

The home page for the Cancer Therapy Evaluation Program (CTEP) division of the National Cancer Institute is a key reference for information on investigational drug use and development. (Table 8). CTEP provides information on policies and guidelines for investigation agents, and includes information, forms, and handbooks for policies regarding investigational drug trials of NCI-sponsored and cooperative group programs.[53]

Publications

Any practitioner who is involved with anticancer drug therapy should have access to standard reference texts as a source of detailed oncology drug information. Examples of standard anticancer drug pharmacology and hematology-oncology disease management textbooks are provided in Table 9. In addition, the oncology pharmacist should periodically scan or review several important medical

Table 10 Selected medical journals of interest to oncology pharmacists

Blood
Cancer Practice (Chemotherapy update column, edited by R. Ignoffo and R. King)
Current Opinion in Oncology
European Journal of Cancer
Gynecologic Oncology
Hospital Pharmacy (Cancer chemotherapy update, by Solimando and Waddell)
Journal of Clinical Oncology
Journal of Oncology Pharmacy Practice
New England Journal of Medicine
Oncology
Seminars in Oncology
The Lancet

journals. A library that contains access to these journals is recommended (Table 10). Since many publishers provide e-mail notification of the current table of contents for selected journals at no cost, a subscription to these services can help the practitioner keep up with new developments.

Online publications

Highlights in Oncology Practice, CA-A Cancer Journal for Clinicians, and Cancer Control Journal are available online free of charge. These high-quality publications provide timely reviews of oncology-related topics that many oncology and general practice practitioners find useful (Table 11). Practitioners will also find that online publications from several academic and government centers can be valuable resources for timely and accurate information regarding alternative and complementary medicines (Table 11).

Treatment updates

The American Society of Hematology (ASH),[54] an organization of clinicians and scientists who are involved in care and research related to hematologic disorders, provides online access to meeting abstracts and its meeting educational booklet, among other educational materials. Practitioners will find that the focus of these materials is primarily in hematologic malignancies and stem cell transplantation, immunology, and hemostasis. The American Society of Clinical Oncology (ASCO),[55] an organization of oncology professionals, also posts searchable meeting abstracts. The ASCO Online Journal Club provides online reviews of key oncology-related articles in the medical literature and can be accessed at the organization Web site. The American Association of Cancer Research[56] allows searchable access to proceedings abstracts and other association-related symposia. Medscape Hematology-Oncology[57] is an outstanding online resource for hematology-oncology practice guidelines, news, conference summaries, and treatment updates. Many full-text reviews and clinical updates are available as well. Registration is required but access to all materials is free. These online sites are a source of new research and drug research findings in hematology-oncology.

PROFESSIONAL NETWORKING OPPORTUNITIES

Education and Training Programs

Specialized oncology pharmacy practice residencies are minimum 12-month postgraduate programs that are designed to develop competencies for practitioners to par-

Table 11 Online cancer-related publications

Publication title	Web site URL	Source
CA-A Cancer Journal for Clinicians	http://www.ca-journal.org/	Peer-reviewed journal from the American Cancer Society
Cancer Control Journal	http://www.moffitt.usf.edu/pubs/ccj/	Published by the H. Lee Moffitt Cancer Center and Research Institute
Highlights in Oncology Practice	http://www.meniscus.com/web/publications/hl/index.htm	Serial publication for healthcare professionals from Meniscus Limited
Other Online Resources	http://nccam.nih.gov/	National Center for Complementary and Alternative Medicine, National Institutes of Health
	http://www.cancer.gov/occam/index.html	Office of cancer complementary and alternative medicine, National Cancer Institute
	http://dietary-supplements.info.nih.gov/	Office of Dietary Supplements, National Institutes of Health

ticipate in care of oncology patients and oncology drug distribution within oncology healthcare systems. The American Society of Health-System Pharmacists has developed accreditation standards for oncology specialty residency programs;[58] individuals who are considering such programs, accredited or nonASHP accredited, should refer to these educational objectives. Specialized pharmacy residency training in oncology will provide the practitioner with the skills and knowledge to work effectively as a multidisciplinary team member to improve patient care.[38] Residency programs provide excellent opportunities for the resident to develop professional relationships with other oncology practitioners.

Oncology specialty review courses are offered by the American Society of Health-System Pharmacists[59] and the American College of Clinical Pharmacy.[60] Some organizations offer mini-traineeships (ASHP, ACCP) to enable practitioners to develop clinical expertise in specialized practice settings; Roxane Laboratories has sponsored a Scholar Program for healthcare practitioners in pain and palliative care for several years. Participation in these review courses and training programs allows practitioners to network with other similarly interested individuals outside their practice setting or institution.

Professional Organizations

The Section of Clinical Specialists of the American Society of Health-System Pharmacists[61] provides networking opportunities for ASHP members who practice or conduct clinical research in oncology pharmacy practice. Members also have input for specialty practice educational programming and receive a networking directory to assist in identifying other practitioners with similar practice and/or research interests.

The Hematology/Oncology Practice and Research Network (PRN) of the American College of Clinical Pharmacy[62] is organized to facilitate dissemination of clinical practice, research, and teaching-related information in hematology and oncology and is also a resource for hematology and oncology expertise among its membership. Members direct and participate in educational programming and network to establish collaborative relationships.

The International Society of Oncology Pharmacy Practitioners[63] was formed at the IV International Symposium on Oncology Pharmacy Practice held in 1995. The mission of this organization is to promote and enhance oncology pharmacy practice worldwide for the purpose of improving cancer patient care. Annual meetings of ISOPP provide national and international networking opportunities for oncology pharmacists.

Several professional oncology-focused organizations are available for pharmacists to join. In particular, oncology pharmacist membership and attendance at annual meetings of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH)[54] are common. There are numerous other organizations related to pain and palliative care, as well as specialty oncology areas. Pharmacists are active members in their institutions' cooperative oncology groups and participate in and attend those meetings as well.

INTERNATIONAL PERSPECTIVES

Trends and issues regarding the safety and efficiency of delivery of patient care services in oncology are similar worldwide, although the structures of these services vary among different healthcare systems and in their maturity. The need for standards for pharmacist training and knowledge in oncology in these treatment settings is widely recognized. Since European hospitals typically have fewer pharmacists than do American hospitals, the provision of comprehensive clinical services in some countries has yet to be accomplished.[39] Some chemotherapy use guidelines have been developed by oncology pharmacy groups. Guidelines for pharmaceutical care of cancer patients, developed by the London oncology pharmacy group, specify that chemotherapy given on nononcology wards should be dispensed by pharmacists who possess some basic clinical training and pharmacists with overall oncology responsibility should oversee such therapy in London.[40]

Policy guidelines for pharmacy services have also been established and adopted by the Society of Hospital Pharmacists in Australia.[41] These guidelines suggest specific areas for which pharmacists should place special emphasis: potential chemotherapy drug–drug interactions, emetic control, analgesia, and gastrointestinal preparations.

SUMMARY AND RECOMMENDATIONS

Oncology clinical pharmacy specialists are well-recognized for their expertise and valued contributions toward improving the efficiency, safety, and outcomes of care provided to patients with malignancies. Formal programs such as oncology specialty residencies offer exceptional opportunities for practitioners to gain the specialized knowledge and skills needed to meet challenging practice

responsibilities in oncology pharmacy practice. Numerous available practice resources such as practice guidelines and reference and online publications facilitate practitioners' use of new knowledge to improve patient care. Despite the wide recognition and appreciation of oncology pharmacy specialists' services, there remains a tremendous need for documentation of the benefits of their services in the medical literature. There is also a need for the public to learn more about the value of oncology pharmacy services. This may be enhanced by having pharmacy organizations develop better public relations and promote the importance of oncology pharmacist certification as a requirement for all institutions that treat patients with cytotoxic chemotherapy.

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Orphan Drugs

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INTRODUCTION

As drug development costs began to rise in the late 1960s and 1970s with new Food and Drug Administration (FDA) requirements for demonstrating relative safety and efficacy, manufacturers of drugs, biologicals, and diagnostic agents faced a dilemma. How could they consider developing drugs that were important medically but not likely to be profitable? Drugs for diseases and conditions that were rare in the United States were one of several—and the most visible—of such drug types. Rarity meant few patients would be available to participate in clinical trials of safety and efficacy under the sponsor's Investigational Exemption of a New Drug (IND) application. Slow patient recruitment into trials increased development time, with the 17-year patent-protection clock ticking. And once the pharmaceutical sponsor received approval for the New Drug Application (NDA) required for interstate marketing, there would be few customers. This generally translated into a low return on investment (ROI). Moreover, the time devoted to testing and gaining approval for a drug for a rare disease was an opportunity cost. Manufacturers would otherwise have devoted the time and resources to products with more favorable market returns.

Six other drug categories were of limited commercial interest. They included products for (1):

1. Chronic diseases, requiring extended testing phases to assess long-term effects, using up critical patent-protection time;
2. Single administration, such as vaccines, requiring separate production facilities, used by many but on a one-time basis, and carrying high liability risks; and diagnostic agents that had relatively low sales volume;
3. Women of childbearing age, presenting unparalleled liability risks;
4. Children and the elderly, both of whom were excluded from clinical testing at the time. Children presented high liability risks and could be difficult to enroll in clinical trials. Elderly people, who often had multiple conditions, were excluded from trials by the FDA because the multiple conditions and drugs used to treat them would confound trial results. (Once a drug was marketed, physicians could prescribe it for these two populations. However, optimal dosing had not been determined, and likely drug interactions in elderly patients had not been identified);
5. Diseases, rare or common, for which the intended drugs were not patentable including shelf chemicals, drugs known to exist, natural chemicals, and drugs for which the patent had expired;
6. Substance abuse or relapse prevention, intended for a population considered to be a high liability risk, uncooperative with treatment trials, and requiring extensive records once marketed; and
7. Developing countries, with the related problems of distributing and paying for products.

Observing that certain drugs could be in common use but were not potentially profitable enough to invite commercial introduction, Provost referred to them in the *American Journal of Hospital Pharmacy* in 1968 as homeless or "orphan" drugs (2). This chapter focuses on orphan drugs for rare diseases. It provides background on the issues and on attempts to deal with them—a description of the Orphan Drug Law, enacted in 1983, to address these issues—and an accounting of progress and problems to date emanating from the law.

BACKGROUND

The 1938 Food, Drug and Cosmetics Act and the 1962 Kefauver-Harris Amendments to it substantially altered drug development in this country. They strengthened the safety and efficacy determinations of drugs, but at cost, one of which was industry disinterest in drugs for rare diseases. The 1938 law required proof of safety after diethylene glycol, used as a sulfanilamide vehicle was found to form lethal quantities of oxalic acid in the body. This resulted in 100 fatalities, mostly children (3). The law required manufacturers to provide evidence that the drugs were relatively safe. For the FDA to keep a drug off the market, however, the onus was on the *agency* to prove that the drug was not safe. The thalidomide disaster changed that situation. Tragic birth defects were reported

DOI: 10.1081/E-ECP 120006169

in infants born to women in Europe and Canada who had taken the drug while pregnant. At the time the news broke, Congress was working on amendments to the 1938 law that required sponsors to provide proof of drug efficacy before receiving market approval. The thalidomide catastrophe propelled Congress to require sponsors also to show proof of safety. To implement these two requirements, the FDA created the IND process requiring sponsors to test for and establish relative safety before embarking on clinical trials to determine drug efficacy. The FDA set up the NDA approval process for ruling on safety and efficacy before the drug could be marketed interstate (4).

An essential interplay developed between patent protection and regulatory requirements. Patent protection became essential for emerging products developed by research-intensive, vertically integrated firms that looked to a few major market winners to survive in this era of increased development costs (5). Patent time used in the IND and NDA premarket stages reduced the time remaining for manufacturers to protect their products, once marketed, against less costly generic drug competition. Drug development also became more expensive. Development costs in the late 1960s and early 1970s, before the FDA amendments became operationally implemented, were estimated to range from a low of $2.7 million to a high of $16.9 million per new chemical entity (NCE) (6, 7). By the late 1970s, the estimate had risen to $54 million (8). Since then, estimates have continued to leap upward: $124 million in the late 1980s, $231 million in 1991, and $500 million today (9, 10).

By the late 1960s and early 1970s, market winners generated most of a company's profits and also helped encourage brand loyalties by prescribing physicians. Other drugs needed to at least break even. Although not blockbusters, these drugs generally were for large markets. Drugs for rare diseases usually did not break even and became therapeutic orphans. They became wards of government and university-sponsored development efforts.

Cancer treatment drugs were among the first wards of government. Even before the 1962 amendments to the Food, Drug and Cosmetics Act, the federal government had developed and maintained a role in stimulating the development of cancer drug treatment that was not being addressed by industry. The National Cancer Institute (NCI) created the Cancer Chemotherapy Program in 1955 with a $5 million Congressional authorization. Congress decided that the NCI should take on the challenge. Impressed with industry's spectacular antibiotics development, Congress recognized that a low ROI was precluding industry's interest in exploiting the early successes in antitumor drugs (antifol aminopterin for acute childhood leukemia and methotrexate for uterine choriocarcinoma). Beginning as a small grant-oriented program to develop antileukemia agents, the program was based on the use of transplantable tumors in syngeneic rodents as a system for testing new drugs. After the NCI drafted an agreement allowing for the trade secret status of data, industry submitted compounds for screening of bioactivity. Within three years, the Cancer Chemotherapy Program had grown into a $35 million industrial contract effort. After a few missteps, when the FDA would not accept the cancer-funded research results as provided, the FDA and NCI developed a clear understanding of how data needed to be provided. From that point until at least the early 1980s, the NCI was involved in the development and/or clinical testing of every antineoplastic drug available in the United States (11–13).

In 1966, the National Institute of Neurological and Communicative Disorders and Stroke, as it was then named, established the Antiepileptic Drug Development Program to develop clinical trial methodologies and then to conduct clinical trials of antiepileptic agents already available in other countries. The program later developed a screening program similar to that of the NCI. The Institute filed INDs for drugs that entered clinical testing, and by 1981, four drugs had commercial sponsorship by the NDA stage (14, 15).

Although most of the federal funding for drug programs by the National Institutes of Health (NIH) was for the development of drugs for rare diseases—cancers and epilepsy—the NIH also devoted funding to development of other categories of orphan drugs. These included drugs to prevent and treat substance addiction and relapse, contraceptives for women of childbearing age, and some vaccines being developed by NIH and by the Centers for Disease Control (now the Centers for Disease Control and Prevention). Before 1983, when the Orphan Drug Act was signed into law, NIH drug development programs and grant-supported research had resulted in 13 drugs for the treatment of rare diseases being approved and on the market. In the 17 years before the Orphan Drug Law, the pharmaceutical industry had developed and marketed 34 drugs or biologicals for use in rare diseases or conditions (16). Ten of these marketed orphan drugs and biologicals had been developed solely by industry without government or university support (17).

The Gathering Storm

Nonetheless, several articles published in medical journals by academic researchers chronicled their plight in formulating new dosages for available drugs or

encapsulating chemical ingredients for clinical tests in patients with rare diseases, because no pharmaceutical sponsor had come to their rescue (18–20). One of these researchers, Cambridge University's John Walshe, proclaimed that this "do-it-yourself" problem had gone far enough and should be placed on a sound commercial basis (21). The FDA published a list of potentially promising therapeutic agents that were under development primarily by academic or government-based scientists who had failed to find commercial sponsors to undertake the costly phase III clinical trials for efficacy, file the NDA, and market the product (22). In 1979, the FDA convened a Task Force on Drugs of Little Commercial Value to determine how to find commercial sponsors. That same year, Louis Lasagna, who was then at the University of Rochester, invoked Provost's notion in an article in the journal *Regulation* by asking who will adopt the orphan drugs (23)?

NIH-funded academic researchers were reporting failed attempts to interest industry in taking on and securing NDA approval for drugs it had not developed. Industry had cited three major problems. First, NIH-funded scientists may not have gathered and analyzed data according to FDA requirements. Second, the trade secret status of data could not be preserved if the researcher had previously published information in the scientific literature. And third, many of the NIH-funded studies were of drugs that were not (or no longer) patentable. The FDA task force recommended that incentives be provided to industry to develop drugs of limited commercial value, but that any profits made from those incentives be returned, in whole or in part, to the government. (24). This arbitration-type approach was based on the assumption that industry would be willing to make trade-offs with the FDA on behalf of these drugs. But this assumption was made in the absence of any indication from industry that this was the case (25).

Although the task force was the first official policy response to the orphan drug situation (apart from the NIH-sponsored research responses), there were several private-sector efforts underway to promote the development and availability of orphan products. The Pharmaceutical Manufacturers Association (PMA, now called the Pharmaceutical Research and Manufacturers of America, or PhRMA) had been seeking sponsors among its member companies for promising orphan therapeutics. And a consumer group, the National Organization for Rare Disorders (NORD), was growing in number (now representing more than 20 million patients and their families) and undertaking efforts to raise public awareness and to help link patients to researchers conducting clinical studies of their diseases or conditions.

Lightning Strikes

A researcher at the Mount Sinai School of Medicine New York, who was seeking a pharmaceutical company sponsor for the drug L-5HTP for myoclonus, appealed to his Congressperson, Elizabeth Holtzman (D-New York) for a legislative remedy to the plight of orphan drug research. She introduced a bill in 1980 to establish the Office of Drugs of Limited Commercial Value to assist the NIH in developing drugs for the treatment of rare diseases (26). Although no action was taken on the bill, the committee heard testimony from a young California man suffering from Tourette's syndrome, a genetically determined neurological condition causing its victims to twitch, tic, and have uncontrollable verbal (and often abusive) outbursts. When haloperidol proved unsuccessful in controlling his symptoms, the patient had tried desperately to obtain and try pimozide, a drug available for the condition in Canada and Europe, but not in the United States.

A Los Angeles newspaper carried an account of the testimony, which caught the eye of the producer of the television series *Quincy*. Before long, a *Quincy* episode was devoted to dramatizing the conundrum of patients trying to cope with Tourette's syndrome and of industry trying to contend with the commercial disincentives to develop drugs to treat these patients. The episode demonstrated that there were no villains and no remedies. In a compelling scene before a Congressional committee, *Quincy* delivered an impassioned appeal to Congress to find a remedy. Shortly thereafter, *Quincy* star Jack Klugman was asked by Congressman Henry Waxman (D-California) to appear at a hearing on an orphan drug bill that was similar to Holtzman's, introduced by her colleague Representative Ted Weiss (D-New York). Klugman testified at the hearing, using the identical appeal he had delivered on the show (27). A *Wall Street Journal* editorial, entitled "Leave of Reality," likened Klugman's appearance before the Waxman subcommittee as an orphan drug expert to having Leonard Nimoy (Mr. Spock on *Star Trek*) testify as an expert on the nation's space program (28). By the end of 1981, Congressman Waxman had introduced H.R. 5238, the Orphan Drug Act.

The orphan drug survey

To find out the current status of development of drugs for the treatment of rare diseases, the subcommittee surveyed the industry, the NIH, and the FDA on three groups of drugs:

1. Products listed by PMA (now PhRMA) member companies as drugs for the treatment of rare diseases

that industry sponsors had marketed or had made available on a compassionate basis to specialists;
2. Drugs and biologicals listed by the FDA as under development, but needing a commercial sponsor for FDA approval and marketing; and
3. Drugs under development by NIH scientists or grantees.

From this survey, the Subcommittee learned that industry had marketed 34 drugs for the treatment of rare diseases extending back to 1965 and had made an additional 24 drugs (under development) available to physicians on a compassionate basis for treating patients with rare diseases. Most (82%) of the marketed drugs were for conditions affecting fewer than 100,000 people in the United States; 10% were for 100,000 to 500,000 people, and the remaining 8% were for up to 1 million people. Industry respondents indicated that substantial federal funding had been provided for research and/or development (R&D) for all but 10 of these marketed drugs.

The picture of disincentives confirmed claims by industry spokespeople sponsors indicated that the ROI for 83% of the drugs was lower than the sponsors' average return for marketed drugs, whereas development costs were higher than average for 12% of these drugs. Other issues cited by industry were the lack of clarity of FDA clinical testing guidelines when small numbers of patients were available and involved. This further eroded the sponsors' ability to estimate the length of clinical testing, and therefore the length of remaining patent protection time, once the drug was approved. Survey data indicated that industry-sponsored marketed orphan drugs took an average of 5.75 years for clinical testing (from filing the IND to filing the NDA). Unpatented orphan products were increasingly unlikely to be submitted for NDA approval, suggesting the importance of having at least some period of market protection. Whereas nearly two-fifths (39%) of industry-sponsored drugs for the treatment of rare diseases had been marketed in the 1960s, even though they were not protected by patent, this fell to 29% by the 1970s. Liability claims had been filed against the manufacturers of one-fifth of the marketed orphan drugs. The promising finding was that one in four industry-sponsored marketed orphan drugs also had a common indication. This suggested that orphan drugs were a relatively good market gamble (29).

Orphan Drug Act's Passage Provides Market Incentives and Regulatory Assistance

Based primarily on Congressional testimony marshaled by NORD revealing that millions of people and their families were profoundly affected by rare diseases and conditions, and on survey data revealing market and regulatory disincentives to therapeutic progress, Congress passed the Orphan Drug Act during a lame duck session in December 1992. Called "the golden egg of the lame duck Congress" by the head of the Generic Pharmaceutical Industry Association (GPIA), the bill was signed into law the first week of January 1983 (30). The act (Public Law 97–414) was supported initially by the GPIA, which had begun seeking sponsors for developed orphan products, and eventually by the PMA after certain provisions were deleted or modified. Provisions in the law, and in subsequent amendments in 1984, 1985, and 1988, addressed market and regulatory issues and provided incentives for pharmaceutical industry development of drugs for the treatment of rare diseases.

The law, as amended, defines a rare disease or condition as one that affects fewer than 200,000 persons in the United States. Alternatively, the disease or condition can affect more than 200,000 persons in the United States, if there is no reasonable expectation that the cost of developing and making a drug available for such disease or condition in the United States will be recovered from U.S. sales of the drug. Therefore, a drug can be designated by the FDA as an orphan by demonstrating applicability of the law's financial criteria, regardless of the total number of people affected in the United States. Major provisions are the availability of two market incentives and the reduction of regulatory barriers. The FDA Office of Orphan Products Development administers nearly all the law's provisions.

One incentive is seven years of market exclusivity granted by the FDA for a specific indication of a product. Exclusivity begins on the date the FDA approves the marketing application for the designated orphan drug and applies only to the indication for which the drug has been designated and approved. An application for designation as an orphan drug for a specific indication must be made before submission of the NDA (or biologic product license application, PLA) for market approval (31). Other sponsors can receive approval for a different drug to treat the same rare disease or can receive approval to market an identical drug for some other orphan or common indication. Market exclusivity, therefore, only precludes a second sponsor from obtaining approval to provide an identical drug for the identical orphan indication for which the first sponsor received exclusive market approval. Initially, market exclusivity pertained only to unpatented products. A 1985 amendment allowed exclusive approval for all orphan drugs, whether patented or not. This change was designed to provide incentives for sponsors of products for the treatment of rare diseases whose patents

would expire before or soon after approval, or in cases in which prior publication (usually by an academic or government scientist) had precluded issuance of a patent.

A second incentive provides tax credits equal to 50% of the costs of human clinical testing undertaken in any given year by a sponsor to generate data required for obtaining FDA market approval through successful completion of the NDA process. The Internal Revenue Service administers the tax credit provisions.

The act provides for the FDA to award grants to support clinical studies of designated orphan products under development. FDA grant funding as of March 2000 from the FDA totaled $126.3 million. From initial funding in 1983 of $500,000 in grants, the grant program peaked in 1994 at $12.3 million and has declined slightly but steadily thereafter, totaling $11.1 million in 1999 (32). Applications are reviewed by outside experts and are funded according to a priority score. The FDA Office of Orphan Product Development provides information at its website (www.fda.gov/orphan/GRANTS/patients) on investigators seeking research subjects. Listed by the name of the disease or condition, information includes a description of the study, criteria for inclusion in clinical trials (such as age, stage of disease, etc.), and contact information on the clinical investigator seeking participants for clinical trials. Patients, their families, or their physicians are able to follow up with the clinical investigator.

To address regulatory barriers the FDA also provides formal protocol assistance when requested by the sponsor of an orphan drug. Although formal review of a request for protocol assistance is the direct responsibility of the FDA Centers for Evaluation and Research (one for drugs, the other for biologicals), the Office of Orphan Products Development is responsible for ensuring that the request qualifies for consideration. A sponsor need not have obtained orphan drug designation to receive protocol assistance.

Table 1 Designated and approved orphan drug products

	Pre-1983	1989	1991	3/2000
Cumulative total approved orphan products	34[a]	36	54	235
Total sponsors of approved orphan drugs[b]	17			110

[a]At the time, these were called drugs for rare diseases, not orphan drugs.
[b]Sponsors identified only for the two endpoints.

Finally, the FDA is required to encourage sponsors to design open protocols for drug availability to patients not included in clinical trials.

The Current Status of Orphan Drugs

The FDA approved 201 orphan products between 1983 and March 2000 (33). In the 17 years since passage of the act, therefore, the number of approved orphan drugs has increased sixfold from the number approved in the 17 years before the act (Table 1). The drugs are classified within 16 therapeutic categories, primarily for the treatment of cancer, infectious disease, AIDS and related conditions, and central nervous system conditions (Table 2). Included in the 201 approved drugs are 24 (12%) that received FDA grant support for clinical trials (34). A list of these grant-supported products is available at the FDA Office of Orphan Products Development website (www.fda.gov/orphan/GRANTS).

The number of sponsors of approved orphan drugs (nearly all of them produced at pharmaceutical or biotechnology companies) has increased from 17 (for the 34 drugs marketed before the act) to 110 as of March 2000. The number of approved drugs per sponsor ranges from one to eight, with a preponderance of one-drug sponsors (Table 3). A total of 813 products have received orphan designations as of March 2000. Sponsors of approximately 25% of these designated products have filed INDs for the products, indicating that they are under active development (35).

Many of the designated and approved orphan products are developed at biotechnology companies. Beginning in the 1970s, molecular biology had begun to spur the creation of biotechnology research companies. These companies reportedly recognized early on that market exclusivity, and lack of competition to develop products for the treatment of rare diseases, provided protection essential to raising venture capital. As a result, orphan drugs are now among biotechnology's most prevalent, and, according to some, most lucrative products. Between 1988 and 1992, biotechnology product designations increased by 31%, from 8 to 39% of total orphan designations (36). In addition to industry, however, sponsors have included a university, an individual researcher, and a state public health unit, which in aggregate sponsored six orphan drugs at the time of approval. Lists of approved and designated orphan drugs can be obtained from the FDA Office of Orphan Products Development. These data suggest that orphan drug development has consistently risen over the years since the law was enacted. Aggregate sales of

Table 2 Approved orphan drugs: Number per therapeutic category[a]

Category	Number of approved orphan products $N = 201$
Cancer	49
Infectious disease	23
Central nervous system	22
Hematopoetic	21
AIDS, AIDS-related	21
Endocrine	18
Inborn errors of metabolism	12
Renal	8
Cardiovascular disease	7
Respiratory	5
Gastrointestinal	5
Bone	3
Immunological	2
Dermatological	2
Antidote	2
Urinary tract	1

[a]Does not include drugs for rare diseases marketed before the 1983 Orphan Drug Law.

orphan drugs have been reported to be more than $1 billion a year (37).

A Resulting Issue: High Pricing for Some Products

By the early 1990s, U.S. sales data collected for 41 of the approved orphan drugs that had been on the market for a year or more indicated that 75% of the products had generated earnings of less than $10 million per drug. Three products had earnings between $10 and $25 million, six drugs between $26 and $100 million, and two products more than $100 million. Biotechnology firms produced four of the 11 drugs with relatively high sales.

Table 3 Approved orphan drugs per sponsor, March 2000[a]

Drugs per sponsor	Sponsors
1	69
2	19
3	6
4	2
5	5
6	2
7	1
8	2

[a]Does not include sponsors of drugs for rare diseases approved before the Orphan Drug Act of 1983.

Those orphan drugs that command high prices have generated intense controversy over whether the market exclusivity provision is creating an unnecessary monopoly, keeping prices artificially high. One example is recombinant human erythropoietin (r-EPO), intended for patients with chronic renal failure-related anemia. EPO eliminates the need for frequent blood transfusions by patients with end-stage renal disease who are undergoing kidney dialysis. These patients are covered under the federally financed Medicare program. Both Amgen Inc. and Genetics Institute applied to the FDA for market exclusivity for their r-EPO products. Amgen was the first to receive FDA approval and market exclusivity. Genetics Institute was the first to receive a patent. On appeal, the court ruled that Amgen had exclusive marketing rights. Sales of r-EPO exceeded $100 million in the first six months of marketing, paid for by Medicare. By 1991, sales totaled $400 million (38).

Human growth hormone (r-hGH), another example, generated sales of $150 million in 1991. Intended to treat approximately 12,000 children in the United States with retarded growth caused by a lack of endogenous pituitary hormone, two companies provide r-hGH. Genentech received FDA market exclusivity in 1985. Eli Lilly received market approval two years later, based on the determination that the two products differed by one amino acid (39,40). But the shared market did not lead to price competition: each company was earning approximately $20,000 per child annually, depending on the dosage needed.

A third example, aerosol pentamidine, generated sales of $130 million in 1991. Helping to prevent *Pneumocystis carinii* pneumonia associated with the human immunodeficiency virus (HIV), the increasing number of users resulting from a rapidly escalating HIV prevalence rate was expected to soon exceed the 200,000 population figure specified in the law. This example, along with the other two, prompted efforts to seek a legislative remedy. A series of amendments were introduced and passed by Congress in 1990 that sought to eliminate orphan status for products intended for use in epidemics and to allow shared market access for identical products developed simultaneously for the same indication, in the hope that this would lead to price competition. The amendments were vetoed (41). As Arno, Bonuck, and Davis present in *Milbank Quarterly*, AIDS treatment drugs exemplify the policy dilemma of how to use the Act to meet the legislative intent of stimulating development of drugs for small patient populations without resulting in prices that make such drugs inaccessible (42).

Another, more recent, example is enzyme therapy for Gaucher's disease, an inborn error of metabolism, treated with Ceredase. The therapy, which requires more than a ton of placenta annually to extract and make the drug, can cost as much as $500,000 per year per person, depending on the dosage needed. A 1996 National Institutes of Health technology assessment panel addressed issues in diagnosis and treatment of the disease and concluded that despite the success of enzyme therapy, treatment is limited by the cost. The panel reported that it was imperative to define the appropriate clinical indications for treatment and to determine the lowest effective initial and maintenance doses (43).

Although the survey undertaken prior to the Act found that retail costs of drugs for the treatment of rare diseases were reportedly higher than the manufacturer's average for 60% of the products marketed before the act, the pricing for some orphan drugs after the act, as exemplified by these examples, is a critically important consequence of the law. This consequence merits continued public scrutiny. It is a sign of progress that for some orphan drugs, accessibility rather than availability is now the challenge requiring creative solutions.

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PROFESSIONAL DEVELOPMENT

Pain Management, Pharmacy Practice in

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INTRODUCTION

All people will experience pain at some point in their lives. On average, most Americans experience one form of pain an estimated three to four times per year. As our population continues to age in the United States, pain management will become an even larger issue. The annual cost of pain to our society was estimated at $79 billion in 1990 with more than 50 million Americans being either partially or totally disabled because of pain.[1]

The lack of appropriate pain management strategies has been significantly documented since the early 1980s. In 1979, the International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage."[2] In 1982, the World Heath Organization (WHO) brought together a panel of cancer pain experts to discuss this worldwide crisis. This group reached the consensus that relief from cancer pain is an appropriate goal for most patients. The WHO placed a high priority on the relief of cancer pain, and another meeting was held in 1984 that resulted in the first publication of *Cancer Pain Relief* in 1986.[3]

This publication was groundbreaking, not only in its discussion of the lack of appropriate cancer pain management worldwide, but in its overall recommendations for managing cancer pain. The concept of the three-step analgesic ladder is introduced, which divides pain ratings into three categories mild, moderate, or severe, with medication selection based on a step-up approach. When this step approach to pain management is employed, up to 90% of all cancer pain can be relieved.

In 1990, the WHO published a report from their expert committee on cancer pain relief and active supportive care.[4] The committee's purpose was to evaluate the current state of cancer care and pain relief, and to provide recommendations and an action plan to improve the overall care of these patients. This publication not only addresses appropriate pain management, but also discusses symptom management for other problems experienced by cancer patients. Since the early 1990s, significant strides have been made in pain management; yet, unfortunately, the WHO goal that every cancer patient has the right to be free from pain has not yet been met.

Ten years after the original publication, an updated version of *Cancer Pain Relief* was published.[5] The update included information from the 1989 publication, as well as any new advances in the management of cancer pain. This publication also included sections on the availability of opioids worldwide and the regulation of health care workers. Even though these publications are specific to cancer pain management, the basic principles can be applied to all chronic pain conditions.

Recently, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) announced the development and approval of new standards for pain management. These standards affect the management of both acute and chronic pain in all health care settings. These standards are included in the 2000–2001 accreditation manuals and are highlighted in this article because they offer numerous opportunities for pharmacists to participate in the pain management process.

Numerous opportunities exist for pharmacists to become involved in pain management. The management of pain can be divided into two major categories: acute and chronic. Examples of acute pain management include the surgical setting or acute injury. Examples of chronic pain management include malignant (cancer) and nonmalignant pain [human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) or rheumatoid arthritis]. This article discusses the opportunities existing for pharmacists in both acute and chronic pain management settings. The goal of this article is not to review the appropriate management of pain, but to provide the reader with an overview of clinical pharmacy involvement in the area of pain management. Therefore, different types of pain management practices are presented and discussed. Important clinical guidelines in these areas are briefly presented. Finally, a comprehensive reference list, of both print media and

DOI: 10.1081/E-ECP 120006309

Internet resources, is also included to facilitate your understanding of clinical pharmacy in pain management.

BARRIERS TO APPROPRIATE PAIN CONTROL

Numerous barriers exist that lead to suboptimal management of pain, and these barriers affect patients, health care professionals, and the health care system. The Agency for Healthcare Policy and Research (AHCPR) published a guideline for the management of cancer pain in March 1994.[6] This publication discusses the major barriers that currently exist to appropriate pain managment. Patients can be reluctant to report their pain, and they may be concerned that pain means worsening disease or that it may distract their physician from treating the underlying cause. Patients may not take their pain medication due to concerns of addiction, worries of opioid side effects, or concerns about becoming resistant to pain medications. Patients and their families can be misinformed regarding pain management. We live in a "just say no" society where opioids are confused with illicit drug use. Patients and their families need to understand the difference between using a medication for a medical reason and using one to maintain a high. A useful analogy is comparing insulin use in diabetics with the use of opioid medications for a painful condition. Both are recognized disease states requiring appropriate management of their disease process.

The health care system has given low priority to pain management due to inadequate reimbursement for provision of services, the legal regulation of controlled substances, and problems of treatment availability or lack of those trained to provide these services. The most significant barrier to pain management is lack of knowledge of the basic principles for appropriate pain management. Several surveys have been conducted in health care professionals, including physicians, nurses, and pharmacists. These studies have revealed a lack of knowledge and education in pain management leading to fear in both prescribing, dispensing, and administering of opioid medications.[7–15]

A survey of 59 questions sent to physicians practicing in the state of Texas revealed many areas of concern when prescribing opioids.[14] Ten percent of those surveyed would withhold opioid medications until a patient in severe pain had either a prognosis of less than 1 year or was terminal. Forty percent were extremely concerned regarding potential addiction. More than one-half falsely believed that opioid addiction is a common occurrence with legitimate prescribing. The physicians surveyed also fear regulatory scrutiny when opioid medications are prescribed for pain control.

Several studies have been published regarding pharmacists' attitudes and knowledge about opioid medication.[8,11,12] These studies have revealed pharmacists as barriers due to insufficient inventories of opioid analgesics, and inadequate counseling of both patients and their families about the importance of using these medications. In the study by Bressler and colleagues, 79% of pharmacists surveyed falsely believed that a patient using sustained release morphine 150 mg every 12 hours would become "addicts" if this dosing level was continued.[11]

Numerous barriers still exist to pain management. These barriers may come from the patient themselves, their physician, or other health care professionals, including pharmacists. One of the most important roles a pharmacist working in pain management can fill is the provision of education, not only to the patient and their family, but also to pharmacists, physicians, nurses, and other health care professionals.

TYPES OF PAIN AND IMPLICATIONS FOR CARE

The exact mechanisms of pain transmission are unknown. Pain is a complex interaction involving receptor stimulation, pain transmission, and response. Pain is generally divided into two categories: acute and chronic. These categories have different characteristics, which affect the approach to treatment. Patients may suffer from both acute and chronic pain at the same time.

Acute pain may manifest itself as a warning when we do something harmful to ourselves. Postoperative pain is also classified as acute pain. Acute pain is considered to be meaningful, linear, and reversible. The therapeutic goal is pain relief, and sedation is often a desirable effect. Medications chosen for treatment of acute pain should have a rapid onset of action and a short duration of action. These opioids are administered on a prn, or as needed basis, usually through an IV with the doses being standardized.[16]

Chronic pain is usually defined as pain that persists for months to years. This may be due to a specific disease state, such as arthritis, diabetes, AIDS, or cancer. Chronic pain is considered to be meaningless, cyclical, and irreversible. The therapeutic goal is pain prevention and sedation is an undesirable adverse effect. Two forms of medication are needed, a long-acting formulation to prevent the pain and a rapid-acting formulation to cover episodes that "breakthrough" the long-acting

opioid. Therefore, the patient takes an opioid on a scheduled basis around the clock and uses supplemental quick-acting opioids to manage additional pain. Dosages are titrated for the individual patient and can vary significantly.[16]

In general, chronic pain is more difficult to manage than acute pain due to the psychological problems caused by unrelenting pain. Chronic pain is usually divided into two categories: malignant and nonmalignant pain. Malignant pain is associated with a diagnosis of cancer and, more recently, HIV/AIDS. The nonmalignant category includes back pain, neuropathic pain, migraines, and many other diagnoses of chronic pain.

Pain Assessment

The first step in managing a patient's pain, whether it is acute or chronic in nature, is assessment. There are numerous methods available to assess pain, including verbal, visual analog, categorical, and faces scales. These methods are discussed in detail in several publications.[6,17–21] The choice of pain assessment scale will depend on the environment in which pain will be assessed, the patient's ability to comprehend the scale, and how detailed the assessment needs to be. Most pharmacists will find a simple verbal scale of 0 to 10, with 0 = no pain and 10 = worst pain imaginable useful.

A component of the new JCAHO standard is documentation of pain assessment and intensity in all patients. In addition, the interventions that are performed based on the pain assessment, such as administration of a pain medication, need to be documented along with the reassessment of the effect of these interventions. Pharmacists can play a key role in developing standardized assessment forms that include recommendations for pain medications based on the results.

Nonpharmacologic Measures for Pain Management

Patients suffering from either acute or chronic pain problems may benefit from nonpharmacologic measures. These measures may also be combined with pain medication. The AHCPR guidelines for the management of cancer pain contains a chapter outlining these options.[6] Nonpharmacologic interventions are divided into behavioral (psychosocial) interventions and mechanical (physical) interventions. Examples of behavioral interventions include biofeedback, self-hypnosis, and relaxation or imagery training. Examples of mechanical interventions include exercise, cutaneous stimulation, and acupuncture.

Behavioral interventions help patients gain a sense of control over their pain management and should be introduced early in the course of their illness. When deciding on the appropriate behavioral intervention, consideration must be given to the intensity of the pain, the expected duration of pain, and the patient's mental clarity, past experience with technique, physical ability, and desire to employ active or passive techniques. Relaxation techniques are easily taught to patients and include focused breathing, progressive muscle relaxation, music-assisted relaxation, and meditation. These techniques are more useful when combined with pleasant images.

The use of physical modalities to manage pain may lead to a decreased requirement for pain-relieving drugs and, just as with behavioral interventions, should begin early in the disease process. Cutaneous stimulation techniques include the application of heat or cold, massage, pressure, and vibration. Exercise techniques should be aimed at preventing immobilization and may include range of motion and stretching. Counterstimulation techniques include the use of transcutaneous electrical nerve stimulation (TENS) devices or acupuncture. These last two techniques have not been formally studied in cancer-related pain.

Use of Nonopioids in Pain Management

Nonopioid agents available for pain management include acetaminophen, nonsteroidal antiinflammatory agents, muscle relaxants, antidepressants, anticonvulsants, corticosteroids, bisphosphonates, and topical preparations, such as lidocaine patches. Depending on a patient's presenting complaints of pain, one of these agents may be an acceptable medication to start. All these medications can also be used in combination with opioid agents. Nonsteroidal agents are useful for pain due to muscle injury or bone metastases. Corticosteroids may be useful in patients suffering from pain due to inflammation or edema, such as spinal cord compression. Bisphosphonates are useful in the management of pain due to bone metastases. The other agents are discussed more in-depth under the section entitled, "Neuropathic Pain Management."

ACUTE PAIN SERVICES

The American Pain Society (APS) published quality assurance standards for relief of acute pain and cancer pain in 1991.[22] These standards were updated and republished in 1995.[17] In February 1992, the AHCPR

published a guideline on *Acute Pain Management: Operative or Medical Procedures and Trauma.*[23] In 1995, the American Society of Anesthesiologists published guidelines for acute pain management in the perioperative setting.[24]

The AHCPR guideline has information about management strategies for various surgeries, including dental, radical head and neck, neurosurgery, chest and chest wall, abdominal, perianal, and musculoskeletal. Other sections of the guideline address pediatric and geriatric acute pain management. A discussion of handling patients with potential addiction problems and those with concomitant disease states is also included. Another important section is recommendations for handling patients with shock, trauma, or burns.

The AHCPR guideline is well referenced and an excellent beginning point for developing acute pain services. The guideline ends with several useful appendices, including a summary of the existing scientific evidence for pain interventions, potential nonpharmacologic interventions, relaxation techniques, and adult and pediatric dosing for nonsteroidal antiinflammatory agents and opioids. Several tools are also included, such as an initial pain assessment form and a monitoring form.

The APS, the American Society of Anesthesiologists, and the AHCPR guidelines outline the basic patient right of being pain free. Improving the quality of pain management includes several key areas. These areas are 1) defining levels of pain that trigger a review of the patient's care plan, 2) providing reference information on the basic analgesic principals that is readily available and near the area where orders are written, 3) educating patients to report pain and provide assurance that patients will receive attentive analgesic care, 4) developing and implementing policies for the use of analgesic technologies, 5) coordinating and assessing these measures, 6) charting pain assessments with a display of the assessment used and relief provided by the intervention, 7) surveying patient satisfaction with pain management, 8) providing specialized analgesic technologies and nonpharmacologic interventions, and 9) periodic monitoring of the efficacy of pain treatments. Unfortunately, even with the publication of these guidelines, data still show that postoperative patients continue to suffer from significant pain.[25]

In 1994, Smythe and colleagues[26] published a study evaluating pharmacy and nursing time requirements, quality of pain control, and cost of patient-controlled analgesia (PCA) versus intramuscular (IM) analgesic therapy. This study showed the PCA therapy provided better pain control than IM therapy after gynecological surgery at an increased cost, but with minimal increases in pharmacy and nursing time.

An article report by Triller and colleagues[27] details their development of a clinical pharmacy program at an existing home health care agency. The pharmacy resident undertook a pain management initiative in this patient population. Patients who had reported pain were identified and, at admission, 53% reported pain interfering with activities of daily living. Twenty-nine percent of these patients were still experiencing pain at discharge from the home health care service. Charts of the next 20 patients admitted to the service who had complaints of pain were reviewed. This review revealed that pain assessments were routinely occurring; however, documentation of interventions was lacking. A committee was formed to develop documentation methods and staff education programs. This article identifies several critical areas for pharmacy involvement in the home care setting, including the management of pain.

A publication by Blau and colleagues focuses on the organization of a multidisciplinary hospital-based acute pain management program.[28] This article stresses that appropriate management of postoperative pain may improve the outcome of surgery, decrease time in the surgical intensive care unit, and therefore allow for earlier discharge of the patient. The first step to initiate a pain management program is to compile an interdisciplinary team. The critical members of this team include physicians, nurses, pharmacists, social workers, and psychologists. The involved physicians in acute pain management are usually anesthesiologists. The role of the pharmacist is as an educational resource, consultant, and technical support. This article does a superb job of describing the basic steps to developing an acute pain management service, and the authors include a copy of the preprinted physician's order form they developed.

Another article describing the implementation of a pain management service at a U.S. Army medical center was published.[29] Even though this project was developed and implemented by clinical nurses, it provides useful information for pharmacists for developing recommendations for an epidural and PCA service. The author also includes copies of their institution's pain assessment flow sheet and pain assessment form. An article describing the application of the American Pain Society's guideline in the management of pain in surgical, oncology, and hospice inpatients in Taiwan was also published.[30] This article contains useful information on performing patient satisfaction surveys on patients undergoing pain management in an inpatient setting, which is another requirement of the new JCAHO standards.

The JCAHO has identified pain management as an import focus for accreditation visits starting in 2000 and 2001. Standards have been developed for ambulatory care, behavioral health care, home care, health care networks, hospitals, long-term care, and long-term care pharmacies.[31] These new standards should help improve acute pain management in these settings.

There are numerous additional helpful references for acute pain management. These include the 1999 *AHSP Therapeutic Position Statement on the Safe Use of Oral Nonprescription Analgesics*,[32] and a review of cyclooxygenase-2 enzyme inhibitors and their role in pain management.[33] For patients with renal or gastrointestinal problems, a helpful discussion of the nonopioid considerations can be found in *Pain*.[34] A useful reference to support the development of acute pain management services is the 1994 article by Lewis and colleagues.[35] This article discusses the physiological consequences of acute pain and the importance of appropriate analgesic therapy.

There are many roles for pharmacists in the management of acute pain. The changes in the JCAHO standards provide an excellent opportunity for pharmacists to become active in the pain management movement. Policies, procedures, and institution-specific guidelines need to be developed and implemented. Pharmacists have essential knowledge of opioid medications, their half-lives, potency, and management of adverse effects. Unfortunately, there have not been many publications by pharmacists discussing their pain management practices. Therefore, pharmacists who successfully implement acute pain services should make every effort to publish their efforts and results.

Pharmacists should be involved in all steps of pain management. This includes the initial development of pain management policies and procedures; development of standardized pain assessment and documentation forms; development of standardized treatment orders, including recommendations to manage adverse effects; education of staff on the implementation of the new pain management standards; and quality assurance efforts to evaluate the policies and procedures.

Some institutions use pharmacists to round on all patients receiving PCA therapy. The patient's total usage over 24 hours is reviewed and changes are recommended when necessary. Other institutions have pharmacists on their pain management teams. These pharmacists see a mixture of both acute and chronic pain patients. Their roles are varied, but include recommendations of adjuvant medications to facilitate in pain relief, patient counseling, health care professionals, and patient education. Patient's who are being discharged should have pain management counseling and a plan developed for home management when necessary.

CHRONIC PAIN SERVICES

Malignant Pain

In March 1994, the AHCPR released a clinical practice guideline for the management of cancer pain.[6] This guideline builds on the previous WHO report published in 1990.[4] This guideline is an excellent reference containing complete information on patient work-up and assessment. Numerous tools for assessment are provided, including the Brief Pain Inventory (Short Form), visual analog scales, and the faces of pain scale. Discussions of nonopioid and opioid doses are included, in addition to conversion tables for switching a patient from one opioid agent to another. Other chapters focus on pediatric and geriatric therapy, and the use of these principles in HIV/AIDS patients.

The AHCPR guidelines recommend using the WHO three-step method for managing cancer pain. Patients should be started on a nonopioid pain medication, such as acetaminophen or a nonsteroidal antiinflammatory agent. If this does not relieve their pain, proceed to the next level of a weak opioid agent, such as codeine or hydrocodone, with or without a nonopioid. If this does not relieve their pain, proceed to the final level of a strong opioid, such as morphine, with or without a nonopioid.

The WHO published an update to their 1990 report on cancer pain relief in 1996.[5] This update presents the advances in pain management since the mid-1980s. This includes new drug entities and dosing recommendations. In addition, it includes a guide to opioid availability from around the world. The American Society of Anesthesiologists published their guidelines for cancer pain management in 1996.[36]

Numerous other publications are available in the area of cancer pain management.[6,37–43] The AHCPR guidelines are an excellent starting place for pharmacists interested in chronic pain management, regardless of it being due to malignant or nonmalignant conditions. These guidelines built on the original recommendations by WHO published in 1990.

Recently, the National Comprehensive Cancer Network (NCCN) published their practice guidelines for cancer pain.[18] This publication has numerous useful figures and tables outlining the process for cancer pain management and serves as an update to the 1994 AHCPR

guidelines. The NCCN guidelines provide the best illustration of today's management of cancer pain.

The biggest impact of these guidelines is changing the basic approach to pain management. Instead of starting all patients out on the first level of pain management (nonopioid), the NCCN guidelines recommend matching the pain medication to the patient's pain level. The patient should undergo a comprehensive pain assessment, including rating their pain using the verbal 0 to 10 scale discussed previously. If their rating is between 1 and 3, the NCCN recommends starting them on a nonopioid; for a rating between a 4 and 6, then begin a short-acting opioid and titrate as needed; and for a rating between 7 and 10, rapidly titrate opioid. At any point, an adjunct analgesic may be added to the regimen.[18]

In addition, the NCCN guideline stresses the importance of beginning a bowel regimen in all patients started on opioids, the use of antinausea medications as required, and psychosocial support and educational activities. In addition, the effectiveness of a pain regimen can be reassessed at 24 to 72 hours, depending on the severity of their initial complaint. This guideline also provides a discussion of surgical or interventional pain management strategies.

A 1999 article discussing a pharmacist-based analgesic dosing service for cancer pain management provides useful information for pharmacists interested in starting an inpatient pain management service in oncology.[44] Northwestern Memorial Hospital has a 33-bed dedicated oncology unit that admits 15 to 20 patients per week from both attending and private physicians. On average, 44% of admitted patients have pain as a continuing problem. A bedside analgesic dosing service (ADS) was developed to educate rotating interns, residents, and fellows on appropriate pain management techniques. This service uses 40% (16 hours) of a full-time clinical pharmacist's hours with rounds being performed each weekday afternoon. The pharmacist is available throughout the day if a patient's pain requires immediate intervention. After-hours and weekend coverage is provided by the pharmacist staffing the oncology satellite pharmacy.

Upon admission, the cancer patient is asked to complete a survey to assess their current pain situation. A copy of the form is provided in the article. Every 8 hours, a nurse records three pain-intensity values on the bedside flow sheet. After a patient is seen and evaluated, recommendations are conveyed orally to the prescribing physician or documented in the progress notes. Verbal orders are obtained when rapid changes are needed to analgesic orders. An education series is provided every month by the ADS attending physician or pharmacist to cover basic approaches to management of cancer-related pain, equianalgesic dosage conversions, use of adjunct medication, and barriers to pain management.

During the first 3 years that this service was in place, 1029 patients with pain were seen by the ADS and 941 (91%) had some kind of interaction with the service's pharmacist, with an average of 3.5 recommendations per patient. These recommendations ranged from correcting medical omissions or incorrect dosing, to changing the route of administration or dosing schedule, to providing agents to manage constipation.

Bonomi and colleagues[45] published an excellent pharmacist guide to quality-of-life assessment in acute, chronic, and cancer pain. The various quality-of-life assessment tools are presented and discussed to help guide the pharmacists in documenting appropriate pain management of these patients. This information can also be used to document the importance of pharmacy involvement in pain management services. Additional helpful tools include two recently published scales, one of which assess symptoms related to malignancy[46] and the scale rating the amount of symptom distress[47] in cancer patients.

Several reviews have also been published regarding the management of pain caused by bone metastases. The most recent advances include the utilization of the bisphosphonates and new radioactive compounds.[48] The American Society of Clinical Oncology (ASCO) published clinical guidelines for the use of bisphosphonates in breast cancer in 2000.[49]

Nonmalignant Pain

The American Society of Anesthesiologists published their guidelines for chronic pain management in 1997.[50] The purpose of these guidelines is to optimize pain control, while minimizing adverse effects and costs, and enhancing functional abilities, physical and psychological well-being, and quality of life. The guidelines also review adjuvant analgesics that are available for pain management, in addition to opioid therapy.

A key component for management of chronic pain, whether malignant or nonmalignant, is the development of a multimodality and integrated treatment approach involving medical, physical, and behavioral therapies. This approach should include physicians (anesthesiologists, neurologists, rehabilitation), pharmacists, social workers, phycologists, and physical therapists.[51] When conventional therapies fail to provide adequate pain control, the patient may require interventional pain management.[52]

More recently, there has been a treatment shift in the management of chronic nonmalignant pain. Increasingly, physicians are including opioids in their management

plans for patients.[53–58] Studies have shown that nociceptive pain responds favorably to opioids, neuropathic pain responds reasonably well, and idiopathic pain syndromes do not seem to respond.[58] This change has led to increased concerns regarding opioid addiction. However, once publication showed that increased medical use of opioid analgesics to manage pain does not appear to contribute to increases in the health consequences of opioid analgesic abuse.[59]

Patients who have a past addiction history need to be closely followed when opioid medications are prescribed. In addition, the health care team may decide to employ an opioid contract in these patients. Whenever possible, these patients should be managed by a pain management clinic and only one physician should be allowed to prescribe opioids.[60]

Model guidelines for the use of controlled substances for the treatment of pain are available.[61] These guidelines recommend the following steps when evaluating the use of controlled substances for pain control: 1) evaluate the patient, 2) develop a treatment plan, 3) sign an informed consent/agreement for treatment, 4) review patient periodically, 5) seek consultation when appropriate, 6) maintain medical records, and 7) comply with controlled substance laws and regulations.

There are numerous publications of recommendations to treat various chronic pain problems. The purpose of this chapter is not to review the various treatments in pain management, but to provide an overview and references. Therefore, included in the following paragraphs is a brief listing of chronic pain conditions and treatments. These articles provide basic reference information for pharmacists interested in pain management.

Treatment recommendations for post herpetic neuralgia were published in 1996 by Kost and colleagues.[62] Several reviews on the treatment of back pain have been recently published.[56,63,64] Treatment guidelines for migraine were published in 1999.[65] In 1998, a review of the treatment of burn pain was published by Ulmer and colleagues.[66]

The APS published a comprehensive new guideline entitled *Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease* in August 1999. For more information about the guideline, write to the APS at 4700 W. Lake Avenue, Glenview, IL 60025-1485, or call 847-375-4715. The cost is $15 for each guideline with a discount on 10 or more copies.

The management of chronic, nonmalignant pain is another area ready for increased participation and education of pharmacists. This involvement should also include community pharmacists who see these patients on a monthly basis. Understanding the appropriate conditions for prescribing opioid analgesics is essential in preventing discrimination against this patient population. In addition, counseling patients on appropriate regimens to prevent opioid-induced constipation should occur in all patients receiving a opioid prescription.

ISSUES IN THE MANAGEMENT OF PAIN IN THE ELDERLY

There are special considerations in the management of elderly patients with malignant and nonmalignant pain. A major concern is the undertreatment of elderly patients in pain, based on a fear of increased toxicity. In 1998, Bernabei and colleagues[67] reported a retrospective study evaluating the adequacy of pain management in the elderly and minority cancer patients being admitted to nursing homes. Thirty eight percent of patients reported daily pain; however, only 26% of these patients were receiving morphine. Patients older than the age of 85 were even less likely to receive weak or strong opioids. In addition, 26% of the patients experiencing daily pain were receiving no medication for this complaint.

This is another area primed for active pharmacy involvement as many of these patients are in nursing homes. These patients are usually undergoing monthly medication reviews by pharmacists who can suggest appropriate dosages and combinations for the management of pain. An article by Shimp[68] estimated that 45–80% of nursing home residents and 20–50% of elderly in the community suffer from pain. This article discusses appropriate selection of therapy and the risks for adverse effects.

The elderly patient usually has multiple medical problems, in addition to pain. A helpful article was published in 1998 by Ruoff for practicing physicians.[69] This article discusses issue with the use of nonsteroidal antiinflammatory and opioid medications in the elderly and patients with comorbid conditions.

NEUROPATHIC PAIN MANAGEMENT

One of the most complex pain states to manage is neuropathic pain, whether it is due to cancer or other chronic illnesses including diabetes, multiple sclerosis, or prior nerve damage. Neuropathic pain may be constant or intermittent and is usually described as burning, stabbing, or lancinating. Patients may exhibit hyperalgesia (increased pain response to noxious stimuli) and allodynia (pain elicited by a non noxious stimuli;[43]). An example of hyperalgesia is an exaggerated pain response to a

poke by a wooden cotton swab. An example of allodynia is an exaggerated pain response elicited by a gentle stroking of the skin or by clothing touching the area.

Treatment usually involves a combination of opioid and nonopioid agents, including antidepressants and anticonvulsants. Several excellent reviews have been published on this topic, and the reader is encouraged to read them.[39,43,69–81] These classes of agents are briefly discussed below.

Chronic pain patients tend to have concurrent depression; however, the antidepressants chosen may not have any pain-relieving properties. Antidepressants that affect one neurotransmitter in the brain, such as selective serotonin reuptake inhibitors have not appeared to be effective in the management of pain in clinical trials. Antidepressants that affect multiple neurotransmitters—namely, serotonin and norepinephrine—have been shown to be effective pain relievers.[82] Two published meta-analyses have shown that tricyclic antidepressants amitriptyline, desipramine, imipramine, and nortriptyline are the most effective treatment for the management of neuropathic pain.[70,78] These publications review the published clinical trial data for all agents available for the management of neuropathic pain.

For patients who are unable to tolerate a tricyclic antidepressant, the choice of agent should consider the patients underlying mental state. If the patient has concomitant depression, another antidepressant such as venlafaxine, nefazodone, or mirtazapine may be the appropriate choice. If the patient does not have concomitant depression, an anticonvulsant agent such as gabapentin may be an acceptable alternative.[73,74,76]

Pharmacists are in possession of unique knowledge regarding these adjunct medications and their mechanisms of action. They can serve as excellent references and educators for health care professionals. Pharmacists who are active in the management of pain can ensure the proper choice of adjunct medications.

CLINICAL PHARMACY PRACTICES IN PAIN MANAGEMENT

Practices in pain management vary greatly among pharmacists. The clinical practice depends greatly on the practice setting. Pharmacists working in acute care or hospital settings may be involved in developing guidelines and standard orders for the appropriate use of PCA pumps. Additional responsibilities may include daily monitoring of all patients on PCA pumps and making recommendations for treatment adjustments. Pharmacists may also round with an inpatient pain management team that provides consultations for pain patients.

Pharmacists in ambulatory settings may work in chronic pain clinics as part of the treatment team. These clinicians perform extensive medication reviews and provide alternatives when treatments fail. Pharmacists who work with diabetic patients may be responsible for managing neuropathic pain.

In the oncology setting, pain management practices vary greatly. The pharmacist may assist in the management of an acute pain crisis with a PCA pump. After an adequate analgesic level is reached, the patient will need to be converted to oral therapy. In other patients, initial regimens can be developed as outpatients. The patient is then followed closely and monitored with medication adjustments when necessary.

In home health care or hospice settings, the pharmacist may be involved in compounding special admixtures for patients. The use of subcutaneously continuous infusions of opioids is also increasing. Pharmacists who review patients' medical administration records in nursing homes can recommend appropriate therapies for pain management.

Regardless of the practice setting, pharmacy opportunities exist in the area of pain management. In most of these settings, patients can be followed and managed over the telephone. Other important issues for pharmacists include the treatment of adverse effects of pain medications, especially constipation.

Patient Assistance Programs

Another excellent area for pharmacists to become involved in pain management is in assisting those patients who are unable to afford their medications. All the pharmaceutical companies have patient assistance programs. These programs require a close relationship with a prescribing physician because the medications are usually shipped directly to the physician's office. There are several web sites devoted to patient assistance programs that are excellent places to start:

- http://www.needymeds.com/MainPage.html (accessed October 2001).
- http://www.cancersupportivecare.com/drug_assistance.html (accessed October 2001).

ORGANIZATIONS FOR PAIN MANAGEMENT

There are numerous organizations devoted to pain management. The decision on which one to join will be affected by the area of pain management in which you are involved. The American College of Clinical Pharmacy (ACCP) and the American Society of Health-System

Pharmacists (ASHP) both have pharmacy-specific groups devoted to pain management. Descriptions of these groups and enrollment procedures can be found at the organization web sites:

- ACCP: http://www.accp.com/index.html (accessed October 2001).
- ASHP: http://www.ashp.org/ (accessed October 2001).

In addition to pharmacy organizations for pain management, there are several national societies devoted to this cause. These organizations are multidisciplinary and provide an excellent resource for pharmacists who want to specialize in pain management. The area of pain management in which you want to specialize will once again affect the organization you choose to join:

- American Academy of Pain Management: http://www.aapainmanage.org/ (accessed October 2001).
- American Academy of Pain Medicine: http://www.painmed.org (accessed October 2001).
- American Chronic Pain Association: http://www.theacpa.org/ (accessed October 2001).
- American Pain Foundation: http://www.painfoundation. org/ (accessed October 2001).
- American Pain Society: http://www.ampainsoc.org/ (accessed October 2001).
- American Society of Addiction Medicine: http://www.asam.org/ (accessed October 2001).
- American Society of Anesthesiologists: http://www.asahq.org/homepageie.html (accessed October 2001).
- International Association for the Study of Pain: http://www.halcyon.com/iasp/ (accessed October 2001).
- National Chronic Pain Outreach Association: http://neurosurgery.mgh.harvard.edu/NCPAINOA.HTM (accessed October 2001).
- National Foundation for the Treatment of Pain: http://www.paincare.org/ (accessed October 2001).

WEB SITES FOR ADDITIONAL INFORMATION AND TOOLS FOR PAIN MANAGEMENT

Purdue Fredrick: http://www.partnersagainstpain.com/ (accessed October 2001).

Abbott Total Quality Pain Management: http://www.abbotthosp.com/prod/pain/pain.htm (accessed October 2001).

City of Hope Palliative Care Resource Center: http://www.cityofhope.org/mayday/ (accessed October 2001).

Mayday Upper Peninsula Project: http://www.painandhealth.org (accessed October 2001).

Medical College of Wisconsin Palliative Care Medicine Program: http://www.mcw.edu/pallmed/ (accessed October 2001).

OncoLink: http://cancer.med.upenn.edu/ (accessed October 2001).

Pain Net: http://www.painnet.com/ (accessed October 2001).

Project on Death in America: http://www.soros.org/death/index.htm (accessed October 2001).

Robert Wood Johnson Foundation: http://www.rwjf.org/main.html (accessed October 2001).

University of Texas Caner Pain Page: http://palliative.mdanderson.org/ (accessed October 2001).

Wisconsin Cancer Pain Initiative: http://www.wisc.edu/wcpi/ (accessed October 2001).

World Health Organization's Cancer Pain Release: http://www.medsch.wisc.edu/WHOcancerpain/ (accessed October 2001).

The web sites of pharmaceutical companies who manufacture medications to relieve pain should be searched regularly for continuing education programs for pharmacists and physicians in both acute and chronic pain management.

CONCLUSION

Even in the twenty-first century the adequate treatment of pain is lacking. There are several reasons for this, including lack of education of health care professionals on the basic principles and knowledge of pain management. Pharmacists can play a vital role in overcoming the undertreatment of pain. Roles include education of health care professionals, patients, and their families; development of clinical treatment pathways for acute and chronic pain; and monitoring and documenting outcomes of pain management, and providing guidance for improvement.

Pain management is a significant expectation of the JCAHO in their year 2000 surveys. Expectations not only include established treatment pathways, but also documentation of outcomes and patient satisfaction. Pharmacists, whether in acute or home health care, community, or ambulatory settings should strive to become leaders in the area of pain management.

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Patient Education/Counseling

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INTRODUCTION

Patient education and medication counseling are an integral part of the healthcare process. The two-way flow of information in these processes is important to improve the quality of care and patient outcomes, and to build patient–practitioner relationships. This article discusses how, through the processes of patient education and medication counseling, pharmacists can ensure that patients take their medications correctly and achieve the most beneficial outcomes of medication use. A variety of methods of communication and counseling skills are presented.

PATIENT EDUCATION

Patient education is a broad term that describes the process through which healthcare professionals attempt to increase patient knowledge of healthcare issues. Patient education can occur in a variety of environments from hospitals and long-term care institutions to physicians' offices, community pharmacies, and other ambulatory care facilities. Patient education may be verbal or written, performed on an individual basis or in groups, and provided directly to the patient or caregiver. Although there are many different types of patient education, the process uses basic communication and educational techniques to achieve its goals of better health and improved health outcomes.

Patient education should be initiated with the first patient contact and is developed with each patient interaction. The process provides for the exchange of information between the patient and the health practitioner. The information gathered is needed to assess the patient's medical condition to further design, select, implement, evaluate, and modify health interventions. The information provided to patients can assist them in making better health decisions. With this two-way flow of information, the process of patient education can assist health practitioners in improving patient outcomes as well as helping to establish or build patient–practitioner relationships.

MEDICATION COUNSELING

Medication counseling is a type of patient education strategy. It is designed to increase patient awareness and comprehension of information related to medication and its use. In general, good patient medication counseling should help the patient to understand why a medication is important in treating their condition, how to use the medication appropriately, and what to expect from the treatment. It is a process that should be highly individualized to meet the patient's specific informational and healthcare needs. Patient medication counseling can be accomplished in a variety of ways, including oral instructions, written information, and/or other forms of audiovisual teaching aids. Counseling may occur between the practitioner and the patient directly, or between the practitioner and the patient's caregiver.

Similar to patient education, medication counseling should be viewed as a process that can improve patient and practitioner knowledge of essential information used to improve health outcomes and quality of life for the patient. The kinds of information conveyed can range from providing very basic levels of information about medicines to very detailed patient-specific information designed to assist a patient with managing a specific medical condition.

Current medical practice relies more heavily on medications than in the past. For these medications to work to their full potential, patients need to take them correctly. Pharmacists are the final health professional contact for most patients receiving prescription medications. Because of this, the community pharmacist is charged with the duty to ensure that patients take their

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006329

medications correctly. Pharmacists and other health practitioners can use patient medication counseling strategies to ensure that patients: 1) take the medication correctly; 2) deal effectively with problems or adverse effects that might arise from taking the prescription; 3) remain compliant with recommended therapies; and 4) know how to assess if the medication is working.

Patient Counseling Methods and Skills

The value and importance of patient medication counseling has been recognized in the literature[1] and by federal legislation (OBRA 90),[2] which has mandated the provision of certain information to patients. When this medication information is combined with the specific needs and perspectives of the patient (e.g., the patient's health beliefs; education level; emotional, physical, psychological, social, and cultural needs), effective medication counseling should result. The responsibility of the health practitioner (pharmacist) is to ensure that the information is appropriate to the patient and is effective in helping the patient to modify or maintain appropriate medication-taking behaviors. *Communication Skills in Pharmacy Practice* provides a complete overview of counseling skills, issues, and methods.[6]

In 1994, the United States Pharmacopiea (USP) established an Ad Hoc Panel on Medication Counseling Behavior Guidelines. This panel was a subgroup of the USP Consumer Interest/Health Education Advisory Panel. The work of the panel resulted in the development of patient medication counseling inventory delineating 35 behaviors that could be part of a patient counseling session.[3] The behaviors are divided into four groups that structure the counseling session into: 1) the introduction of the session; 2) the content of the session; 3) the process followed; and 4) the conclusion of the session. The behaviors (detailed descriptions are available at the USP web site[3]) include the following:

- Conducts appropriate counseling by identifying self and the patient or the patient's agent
- Explains the purpose of the counseling session
- Reviews patient records prior to counseling
- Obtains pertinent initial drug-related information (e.g., allergies, other medication, age)
- Warns patient about taking other medication, including over-the-corner drugs, herbals/botanicals, and alcohol, which could inhibit or interact with the prescribed medication
- Determines whether the patient has any other medical conditions that could influence the effects of this drug or enhance the likelihood of an adverse reaction
- Assesses the patient's understanding of the reason(s) for therapy
- Assesses any actual and/or potential concerns of problems of importance to the patient
- Discusses the name and indication of the medication
- Explains the dosage regimen, including scheduling and duration of therapy when appropriate
- Assists the patient in developing a plan to incorporate the medication regimen into their daily routine
- Explains how long it will take for the drug to show and effect
- Discusses storage recommendations and ancillary instructions (e.g., shake well, refrigerate)
- Tells patient when they are due back for a refill
- Emphasizes the benefits of completing the medication as prescribed
- Discusses potential (significant) side effects
- Discusses how to prevent or manage the side effects of the drug if they occur
- Discusses precautions (activities to avoid, etc.)
- Discusses significant drug–drug, drug–food, and drug–disease interactions
- Explains in precise terms what to do if the patient misses a dose
- Explores with the patient potential problems in taking the medication as prescribed (e.g., cost, access)
- Helps patient to generate solutions to potential problems
- Provides accurate information
- Uses language that the patient is likely to understand
- Uses appropriate counseling aids to support counseling
- Responds with understanding/empathic responses
- Presents facts and concepts in a logical order
- Maintains control and direction of the counseling session
- Probes for additional information
- Uses open-ended questions
- Displays effective nonverbal behaviors
- Verifies patient understanding via feedback
- Summarizes by acknowledging and/or emphasizing key points of information
- Provides an opportunity for final concerns and questions
- Helps patient to plan follow-up and next steps

This inventory of behaviors was designed to be relevant to a wide variety of counseling situations and can provide a framework for pharmacists and other health professionals in providing patient medication education and counseling.

It should be noted that, for any given patient counseling encounter, any combination of these items

may be included to focus attention on the specific needs of the patient and may also include verbal instruction, written information, or demonstration. The practitioner should keep in mind that the patient's ability to use written information effectively may be limited, depending on the nature of the written information. The USP Drug Information Advice for the Patient[7] provides an excellent resource for patient-oriented material, including pictograms for use with hearing- or language-impaired patients. Also, demonstration, such as with the use of inhalation aerosols or insulin injections, may be used to either educate or verify how a patient is using one of these products.

In addition to pharmacist–patient education, there are a variety of other resources available for use in patient teaching. These include company-prepared materials such as videotapes and audiotapes for patients, booklets, leaflets, and even periodic newsletters. For some disease states, pharmaceutical companies have formed virtual support groups where questions can be discussed online with various health professionals. In addition, there are texts prepared to assist the pharmacist in determining the most appropriate information for a patient encounter such as the *Patient Counseling Handbook*.[8]

Communication Skills and Counseling Methods

There are many different techniques that pharmacists and other health professionals may use to provide patient medication counseling. In addition to the information requirements of patient medication counseling, the communication skills employed by pharmacists are important to good patient education. In particular, skills that build rapport (proper introductions, learning and using patient names, talking in lay terms, etc.), good listening skills (summarizing, paraphrasing, and the use of empathic responses), appropriate body language (tone of voice, eye contact, posture, etc.), and interactive techniques (use of open-ended questions) are key to good pharmacist–patient communication. Structured counseling strategies that have been developed for pharmacists to enable them to provide better care are presented in the following paragraphs.

Interactive patient counseling

Interactive patient counseling methods[4,5] use open-ended questions to determine what the patient knows about the medical condition and its treatment. For example, by asking "What did your doctor tell you this medication was for?", the pharmacist can discern if the patient knows what condition is being treated. Other questions can be employed to assess the patient's knowledge of the medication directions, "How did your doctor tell you to use this medication?" and expected outcomes, "What did your doctor tell you to expect." Once the existing knowledge of the patient is determined, the pharmacist can fill in any information gaps that are identified. Verifying the patient's understanding of the information communicated will then complete the counseling. Counseling in this manner can improve the efficiency of medication counseling because only information that the patient does not already know is provided. It also ensures and reinforces patient knowledge through the verification process.

The PAR technique

In medication counseling there are often times when patients can present with challenging or difficult to handle situations. These situations can arise from behavior on the part of the patient or the pharmacist. Some patient examples might include when a patient is in a hurry to get back to work, has a sick child, has a hearing impairment, or does not speak English well. On the pharmacists side of the process, challenging situations could arise as a result of a busy pharmacy, interruptions, or lack of confidence about the ability to counsel. These challenging situations may be the result of either functional (e.g., disability such as loss of hearing, a patient who is a wheelchair user) or emotional (e.g., a patient who is angry, in a hurry, or who is confused by their problem) barriers. Any barriers to communication that are present must be resolved before effective counseling can occur.

When confronted with a potential or apparent communication barrier, the goal of the pharmacist should be to react and respond to the patient in ways that defuse tension to effectively remove barriers. The PAR (Prepare, Assess, and Respond) technique,[4] originally developed in the field of psychology, involves preparing for each patient encounter, assessing situations before and after they arise, and responding to patients in a manner that removes any barrier to communication.

To effectively prepare for a patient encounter, a pharmacist examines the environment in the pharmacy setting, the prescription, the patient profile, as well as any personal knowledge of the patient to identify potential barriers to communication before they arise. Once a problem has emerged or been identified during a counseling session, the pharmacist must assess it accurately. To assess, pharmacists must identify possible emotional or functional barriers. This may require careful observation

and attention to the patient to determine the exact nature of the problem.

Once the pharmacist has identified and assessed a problem that has been identified, it is necessary to respond to the patient in an appropriate manner. The PAR technique suggests that the use of empathic responses, reflecting patient feelings, and the use of probing questions to encourage patients to talk will help in resolving communication barriers. Pharmacists should keep in mind that the ultimate goal is to ensure that the patient takes the medication correctly. This can be accomplished through medication counseling only after any communication barriers have been removed. Acting in this manner, rather than reacting defensively to the patient, can open the lines of communication and facilitate patient education.

Counseling for compliance

A process referred to as the RIM (Recognize, Identify, and Manage) technique[4] structures a process for pharmacists to use to help patients solve compliance problems through patient education. To maximize patient compliance with recommended therapies, pharmacists can learn to recognize objective and subjective forms of evidence to determine if the patient has a potential problem with medication compliance. Some examples of objective evidence might include reviewing the patient profile to identify problems with the refill record, the presence of complex regimens, or patients with high-risk disease states. Subjective evidence, for example, might involve comments from patients expressing uncertainty about the effectiveness of their therapy, questions about the dose prescribed, or hesitation when asked how the medication may be working.

Using various forms of empathic or reflecting responses, universal statements, and probing questions, pharmacists can learn to identify the specific causes of noncompliance. For example, questions such as "It sounds like you are unsure about how to take this medication" (reflecting response), "Tell me more about how this medication makes you feel dizzy" (probing question), and "Many patients will feel sleepy after taking this medication" (universal statement) can be useful in determining the nature of the patient's problem.

Once a compliance problem has been identified, pharmacists can use patient education to help patients to manage their medication regimen better. For example, providing information to alleviate patient fears about side effects, affirming the need for a medication, assurance about benefits, or even helping the patient to plan a typical day to include taking their medication on schedule.

CONCLUSION

Patient education and medication counseling are an integral part of the healthcare process. The two-way flow of information in these processes is important to improve the quality of care and patient outcomes, and to build patient–practitioner relationships. Through medication counseling, pharmacists can ensure that patients take their medications correctly. Knowledge of a wide variety of communication and counseling skills is important to successful patient education. Specific methods are available to assist pharmacists in providing effective counseling and patient education.

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Patient Satisfaction

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INTRODUCTION

Patient satisfaction is a commonly used measure to help assess how well healthcare providers are meeting the needs of their patients. Donebedian states that satisfying patients is one important indicator of quality care, because it demonstrates the ability of the provider to meet expectations and values of the patient.[1] Industry reports on managed care organizations include patient satisfaction as one measure of service quality.[2–4] However, the science of measuring patient satisfaction is yet in its infancy.

WHAT IS SATISFACTION?

Oliver defines satisfaction as "an individual's *judgment* about the extent to which a product or service provides a pleasurable level of consumption-related fulfillment."[5] Stated simply, satisfaction results from an *evaluation* of a product or service that nets some emotional reaction. A judgment is made by an individual as to how well the service was provided, and this judgment results in pleasure if satisfaction occurs or displeasure if dissatisfaction occurs.

Satisfaction is not to be confused with dimensions of quality such as 1) quality of conformance or 2) quality of design. *Quality of conformance* is the consistency of how the product is manufactured or the service is delivered. For example, pharmaceutical tablets are manufactured to fit within FDA standards for dissolution. Each batch is tested to determine if tablets within that batch fit standards. *Quality of design* is how well the product or service meets the needs of consumers or how well the product or service compares with those of competitors in the eyes of the consumer. In the pharmaceutical tablet example, the manufacturer would evaluate the quality of design by comparing the clinical outcomes provided by the product to the desired outcomes of the patients. Such factors as returning to "normal" health or avoiding side effects would be used in the evaluation of quality of design. Finally, a pharmaceutical company must compare its product with those of competitors from the viewpoint of the consumer. The question to ask would be, "Is my product perceived by consumers as safer and more effective than my competitor's product?"

In contrast to how quality is measured and evaluated, satisfaction is specific to the individual and is based on the perceptions and judgments of individuals. It follows, then, that *patient satisfaction* is an individual's judgment about the extent to which a healthcare product or service provides a pleasurable level of consumption-related fulfillment. In the recent literature,[6] satisfaction has been conceptualized in four ways: 1) performance evaluation; 2) disconfirmation of expectations; 3) affect-based assessment; and 4) equity-based assessment (Table 1).

SATISFACTION AS PERFORMANCE EVALUATION

Patient satisfaction can be viewed as a "personal evaluation of healthcare services and providers."[7] Ware and colleagues developed the Patient Satisfaction Questionnaire (PSQ) using a performance evaluation approach. In such an approach, service characteristics are divided into categories (e.g., interpersonal characteristics, accessibility). Then, individuals are asked to respond to each statement about the service on a Likert-type scale usually ranging from "strongly agree" to "strongly disagree."

Ware and colleagues viewed patient satisfaction as a multidimensional construct in which distinct features of care are assumed to influence individuals' attitudes toward providers and services, with each of these features possibly having a different effect on satisfaction. Much of the literature on patient satisfaction has focused on identifying salient characteristics of healthcare services for evaluation by individuals.[8]

Viewing patient satisfaction as performance evaluation is most useful for services that have characteristics in-

Table 1 Conceptualizations of satisfaction

Conceptualization	Focus	Strengths	Weaknesses
Performance evaluation	Salient characteristics of a service.	Can evaluate specific characteristics of a service.	Characteristics are selected by the researcher and might not be reflective of individuals' views.
Disconfirmation of expectations	Cognitive appraisal of a service experience.	Provides an understanding of the psychological process of service evaluation.	Results are sensitive to the type and level of expectations used for the study.
Affect-based assessment	Emotional response to a service and resultant actions by the individual.	Allows the investigation of the emotional responses to services, especially in the absence of prior expectations.	Might be applicable to short-term evaluations but not to long-term evaluations.
Equity-based assessment	Fairness in what is gained compared with what it cost the individual.	Allows the investigation of the relationship between inputs and outputs of the individual and the service provider.	Assumes that fairness is the key determinant of satisfaction.

(From Ref. [6].)

dividuals can identify and understand. However, individuals might not have the expertise to assess unfamiliar or ambiguous services. In these instances, individuals might base their evaluations on their expectations of whether or not such a service should be offered to them or on how the service experience makes them feel.

SATISFACTION AS DISCONFIRMATION OF EXPECTATIONS

In his conceptual article, Oliver described satisfaction as a result of one comparing an expectation to the actual service experience. This gap between the expectation and service experience then can impact how one feels about the service experience or the individual's satisfaction with the service.[9] The disconfirmation of expectations model that Oliver describes in his paper has been tested and validated by various researchers.[10–14] This model states that individuals compare their experiences with the service to expectations. These expectations serve as a reference point.[9] Although many researchers have accepted this view of satisfaction, they have held different opinions about which expectations, or comparison standards, are most pertinent and about which interrelationships among variables are most important in the satisfaction process.[9,15]

SATISFACTION AS AFFECT-BASED ASSESSMENT

Satisfaction also has been viewed as a pleasurable response to a service encounter. This type of conceptualization takes into consideration that individuals with moderate expectations of a healthcare service will likely be indifferent if those expectations are met. However, individuals with high expectations of a healthcare service might be delighted if a healthcare provider met their high expectations. Thus, the focus in this conceptual framework is the degree of affective response and not only how well expectations were or were not met. Also, Kucukarslan, Pathak, and Segal showed that this conceptual view of satisfaction can be very useful in cases when individuals have no prior expectations of a healthcare service.[16] In the healthcare domain, individuals often do not know what to expect when experiencing a healthcare service. In these cases, how a person feels would be an appropriate way to gauge patient satisfaction because knowledge about the service and prior expectations about the service are absent.

SATISFACTION AS EQUITY-BASED ASSESSMENT

A fourth conceptualization of patient satisfaction is an equity-based assessment. This is a comparison of one's outcomes versus inputs with respect to someone else's outcomes versus inputs.[5,17] The resulting perception of fairness has a direct relationship to satisfaction. Individuals who perceive that a service provider has gained more than they have are likely to be less satisfied. Studies show that perceptions of fairness increased as the differences between inputs and outputs increased in favor of the individual.[18,19]

Such an approach to understanding patient satisfaction assumes that fairness is the key determinant of patient satisfaction. An understanding of the key inputs and outputs of a healthcare service are required as well. There are only a few examples of this approach in the healthcare literature,[16,19] but it could be quite useful in situations where equity is a primary consideration (e.g., satisfaction with insurance coverage for healthcare services).

TOOLS TO MEASURE PATIENT SATISFACTION

No single, standard conceptualization of patient satisfaction is applicable to all situations. When selecting a conceptualization of satisfaction, the investigator must identify the research question. For example, if the primary research objective is to compare service providers in terms of how well individuals rate specific aspects of service performance, an experience-based evaluation of performance would be appropriate. If the research is focused instead on the relationship between individuals' evaluation of a service and their future commitment to the service provider, a satisfaction measure that reflects evaluative and affective reactions by the individual would be appropriate.

Also, one should remember that patient satisfaction might not be the most relevant outcome for study. Performance, quality, loyalty, complaining behavior, trust, or some other outcome might be more useful for decision making, planning, implementation, and evaluation related to healthcare products and services. It is important to link the construct being measured to the problem or decision that the study results will help address.

Two popular patient satisfaction measures for which psychometric properties have been investigated and reported include 1) Ware et al.'s Patient Satisfaction Questionnaire (PSQ)[7,20,21] and 2) MacKeigan and Larson's Patient Satisfaction with Pharmacy Services Questionnaire (PSPSQ).[22,23]

Ware et al.'s Patient Satisfaction Questionnaire (PSQ),[7,20,21] and related versions, has become one of the most widely used measures of satisfaction with medical care.[24] The most recent version, called the Short-Form Patient Satisfaction Questionnaire (PSQ-18), can be obtained from RAND Corporation, Santa Monica, California.[24] This version contains 18 items that focus on seven distinct areas: 1) general satisfaction; 2) technical quality; 3) interpersonal manner; 4) communication; 5) financial aspects; 6) time spent with doctor; and 7) accessibility/convenience. Acceptable reliability and validity have been reported for this measure.[24] It constitutes a widely used and accepted measure of patient satisfaction with medical care.

A widely accepted example of patient satisfaction measurement that is specific to pharmacy services is MacKeigan and Larson's Patient Satisfaction with Pharmacy Services Questionnaire (PSPSQ).[22,23] Introduced in 1989,[22] MacKeigan and Larson patterned their measure after Ware et al.'s Patient Satisfaction Questionnaire (PSQ).[7] Eight dimensions of pharmacy services were used for the questionnaire: 1) explanation; 2) consideration; 3) technical competence; 4) financial aspects; 5) accessibility; 6) drug efficacy; 7) nonprescription products; and 8) quality of the drug product dispensed. Over time, this measure has been tested and revised. In 1994, Larson and MacKeigan[23] further refined their questionnaire into a 33-item measure reflective of seven dimensions: 1) explanation; 2) consideration; 3) technical competence; 4) finance; 5) accessibility; 6) product availability; and 7) general. Reliability and validity of this measure are supported,[22,23] and it has been used in the pharmacy services domain.[25,26]

CONSIDERATIONS FOR MEASURING PATIENT SATISFACTION

Because a number of conceptualizations of patient satisfaction can be used, the measurement of patient satisfaction must fit the context of the overall research process. A research process proposed by Churchill[27] involves six stages: 1) formulate the problem; 2) determine the research design; 3) design data collection method and forms; 4) select a sample and collect the data; 5) analyze and interpret the data; and 6) prepare the research report. Each stage is linked, and decisions made at one stage will affect decisions made at other stages.

When investigating patient satisfaction, one must also consider the requirements and limitations imposed by the research process itself. For example, the purpose of the research, potential users of the data, time and money available for the study, the population of interest, and the data collection methods will all influence the type of satisfaction measure determined to be the most appropriate. Limitations in these factors must be recognized, whether a new measure of patient satisfaction is being developed or an existing measure is being used.

Because the meaning attributed to a satisfaction measure by the investigator may not be the same as the meaning imputed to it by the respondents, a systematic process for developing measures should be followed that includes: 1) specifying the domain of the construct; 2) generating a pool of items and determining the format of the measure; 3) having the initial pool of items reviewed by experts; 4) considering inclusion of validation items;

5) administering items to a development sample; 6) purifying the measure; and 7) optimizing the practicality of the measure (see Ref. [28] for a useful summary of this process).

When using existing measures of satisfaction or when developing new measures for a specific research purpose, acquiescent responding can be a problem. Acquiescent responding is the tendency to agree with statements of an attitudinal nature regardless of the statement's content.[24] To overcome this problem, the use of a balanced multiple-item measure, asking several positively worded questions and several negatively worded questions, is crucial to the measurement of patient satisfaction. This method tends to cancel out any systematic tendency to simply agree with items contained in the questionnaire.[24]

Finally, when comparing satisfaction among groups of individuals who belong to different health plans or access different care providers within a health plan, it is important to control for case-mix. *Case-mix* refers to the different patient attributes that might be apparent in different settings.[24] To the extent that patients self-select or are assigned to different comparison groups in non-random ways, comparisons of satisfaction ratings may be biased by factors other than the provision of the healthcare services in the compared groups. For example, relationships between health status and patient satisfaction have been reported.[24] Thus, it is often prudent to control for the effects of health status when comparing patient satisfaction among or between groups. Other factors might account for differences in satisfaction scores depending on the question being addressed in the study. Case-mix control variables such as age, gender, socioeconomic status, disease severity, physical functioning, service expertise, or service provider familiarity also should be considered for inclusion in the study. Methods used to control or adjust for case-mix variables can then be used (e.g., restriction, stratification, matching, statistical adjustment). Johnson[24] has written a useful summary of these methods.

CONCLUSION

Patient satisfaction is an individual's judgment about the extent to which a healthcare product or service provides a pleasurable level of consumption-related fulfillment. In the recent literature, patient satisfaction has been conceptualized in four ways: 1) performance evaluation; 2) disconfirmation of expectations; 3) affect-based assessment; and 4) equity-based assessment.[6] Commonly used patient satisfaction measures include Ware et al.'s Patient Satisfaction Questionnaire (PSQ)[7,20,21] and MacKeigan and Larson's Patient Satisfaction with Pharmacy Services Questionnaire (PSPSQ).[22,23] However, no single standard measure of patient satisfaction is applicable to all situations. We suggest that an existing measure of patient satisfaction, with demonstrated reliability and validity, should be used if it fits the construct domain of the study. Whenever a new satisfaction measure is needed, its conceptualization should be defined carefully and a systematic process for developing a measure should be followed.

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Pediatric Dosing and Dosage Forms

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INTRODUCTION

The administration of medications to pediatric patients is in many ways difficult because health care providers and parents are faced with many challenges not experienced, or experienced to a lesser degree, than when medications are prescribed for and taken by adults. First, less information is available about the use of most medications for pediatric patients. In fact only about 20% of drugs marketed in the United States have labeling for pediatric use.[1] Milap Nahata, in a 1999 article on pediatric drug formulations, stated that "only five of the 80 drugs most commonly used in newborns, and infants are approved for pediatric use".[1] Second, many drugs that are used for some pediatric patients are not in appropriate dosage forms for use by children. This includes even some medications approved for use in pediatric patients. These issues have resulted in many questions that need to be answered about drug administration to pediatric patients. For example, is the drug approved for use in pediatric patients and in what age groups? If not approved, is there scientific information that enables us to determine whether the drug is safe and effective for pediatric patients of various ages? If the drug is available commercially for pediatric use, what dose should be administered and how frequently? What route should be used for administration, and what dosage form selected? If the drug is not available in an appropriate dosage form for childhood use, can it be prepared extemporaneously? Are there stability studies, palatability tests, clinical data in children, etc. that pertain to the extemporaneous formulation? How should the drug be monitored for effectiveness as well as for adverse effects? Information determined in adult medication studies may not be applicable to pediatric patients because of pharmacokinetic and pharmacodynamic differences as well as differences in disease states for which a particular drug might be used. Many questions about the use of particular drugs in various age groups of pediatric patients can only be answered through well-designed, randomized controlled studies in pediatric patients who need certain medications for particular health problems.

HISTORICAL BACKGROUND

In 1997, the Food and Drug Administration (FDA) proposed new regulations for how pharmaceutical manufacturers would access safety and efficacy of certain new drugs that could have pediatric indications.[1,2] Thereafter, the FDA and the American Association of Pharmaceutical Scientists (AAPS) held a conference with academicians, pharmaceutical industry representatives, and U.S. Pharmacopeia (USP) representatives to discuss these proposed FDA regulations.

The FDA Modernization Act (FDAMA) of 1997 contains within it financial incentives for the development and marketing of drugs that could be used for pediatric patients.[3] Some of these incentives include an extension of 6 months on market exclusivity and waiving fees for supplemental applications needed for receiving the approval of drugs for pediatric use that are already approved for adult use. In addition, the FDA published a list of drugs approved in adults for which additional pediatric data may produce health benefits for pediatric patients.[4] For drugs on this list, FDA may ask a pharmaceutical manufacturer why it has not sought approval of a particular drug for pediatric use.

Various medical and pharmacy organizations have worked hard throughout the years in their efforts to better educate children, parents, educators, and health care providers about the medications and their appropriate use. Indeed, individuals who help care for children may not be adequately trained to educate children about medications that they need to use. In June 2000, the USP developed three target initiatives that related to pediatric medication use: principles for educating children about their medications, guidelines for developing and evaluating information for children, and developing specific curricular information in a modular format.[5] The USP position

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006418

about educating children about medications may be found on their website (www.usp.org). The following information pieces have been developed by the USP:[5]

- *Guide to Developing and Evaluating Medicine Education Programs and Materials for Children and Adolescents* (joint publication of the American Health Association and USP).
- *A Kid's Guide to Asking Questions about Medicines.*
- *Teaching Kinds about Medicines.*
- *Talking to Children about Their Medicines* (pamphlet developed jointly by Pfizer and USP to be disseminated to pediatricians and children's families).
- An Annotated Bibliography of Research and Programs Relating to Children and Medications.

The USP worked with the National Center for Health Education in New York to develop educational materials that can help school systems nationwide to know more about medications that students may need to take. The USP also adopted the following resolution to address the work that needs to be done in the area of health education:[5]

> Facilitate and contribute to the development of a rational school medicines policy, including guidelines for student, faculty, and staff medicine education, for acquisition, transport, storage, administration, use, and disposal of medicines; for protection of privacy; and for record-keeping in primary and secondary schools. Initiative should be undertaken in collaboration with appropriate partners.

The USP worked with the National Institute of Child Health and Human Development (NICHD) to develop a list of drugs for which more pediatric information is needed to insure proper use in children.

This overview of pediatric dosing and dosage forms covers issues that peditric health care providers face daily, such as age-related drug pharmacokinetic and pharmacodynamic changes that occur secondarily to physiologic changes in maturing neonates, infants, children, and adolescents that can affect drug absorption from various routes of administration as well as drug distribution, metabolism, and elimination. To be more knowledgeable about pharmacokinetic changes, therapeutic drug monitoring (TDM) must be undertaken for drugs with narrow therapeutic indexes and for those for which pharmacodynamic data (i.e., pharmacologic response that correlates to the drug concentration at the receptor site) correlates with pharmacokinetic information. Also addressed will be drug administration by various routes including intravenous (i.v.), oral (p.o.), intramuscular (i.m.), subcutaneous (s.c.), percutaneous, rectal, otic, nasal, ophthalmic, and inhalation. Another issue discussed is product selection for pediatric patients.

To better understand changes in drug disposition, the pediatric population needs to be categorized into various groups (Table 1) because children vary markedly in their absorption, distribution, metabolism, and elimination of medications. This occurs because neonates, infants, children, adolescents, and adults have different body compositions (i.e., as to their percentages of body water and fat) and have their body organs in different stages of development.

PEDIATRIC PHARMACOKINETICS AND PHARMACODYNAMICS

Effect of Developmental Physiologic Changes on Pharmacokinetics and Pharmacodynamics of Drugs

Rational pediatric pharmacotherapy is primarily based on the knowledge about a particular drug, including its pharmacokinetics and pharmacodynamics, that may be

Table 1 Pediatric age groups terminology

Terms	Definition
Gestational age	Time from the mother's last menstrual period to the time the baby is born; at birth, a Dubowitz score in weeks gestational age is assigned, based on the physical examination of the newborn
Postnatal age	Age since birth
Postconceptional age	Age since conception, i.e., gestational plus postnatal age
Neonate	First 4 weeks or first month of life
Premature neonates	Born at less than 37-weeks gestation
Fullterm neonates	Born between 37- and 42-weeks gestation
Postterm neonates	Born after 42-weeks gestation
Infant	1 month to 1 year of age
Child	1–12 years of age
Adolescent	12–18 years of age

modified by physiologic maturation of the child from birth through adolescence. Physiologic changes that occur can affect drug absorption, distribution, metabolism, and elimination. The most dramatic changes occur during the neonatal period.

Oral Absorption

Drug absorption from the gastrointestinal (GI) tract is dependent on patient factors, physicochemical properties of the orally administered drug, and the drug formulation. Patient factors that affect GI absorption include absorptive surface area, maturation of the mucosal membrane, gastric and duodenal pH, gastric emptying time, GI motility, enzyme activity, bacterial colonization of the GI tract, and dietary intake, including the specific gastric content status at the time when a medication is ingested.[6–8] Patient factors are influenced by rapid maturational changes that occur throughout early childhood, but which occur primarily during the first few months of life.

Most drugs are absorbed across the GI tract by passive diffusion, but a variety of drug physicochemical factors influence the extent of absorption. These factors include molecular weight, lipid solubility, ionization as well as disintegration and dissolution rates.[7] In addition, drug absorption may be dependent on the dosage form selected (e.g., a liquid, a tablet that may need to be crushed, or a sustained-release product), and the particular brand selected. For time-release preparations, the release characteristics must also be taken into consideration.

Gastric pH

When examining patient-specific factors such as gastric pH, which affect oral absorption, it should be noted that infants born vaginally who are at least 32-weeks gestation, usually have gastric pHs between 6 and 8 at birth.[7,8] Gastric pH then falls rapidly within a few hours after delivery to a pH of less than 3.[7,8] The initial gastric pH is alkaline compared to that of adults and results from the presence of amniotic fluid in the infant's stomach.[9,10] Thereafter, gastric pH remains acidic until approximately day 10, then a nadir in acid production occurs between days 10 and 30 of life. Then gastric acid production begins to increase, but gastric pH and maximal gastric output may not mirror that of adults on a per kilogram basis until after the neonatal period.[7]

Gastric emptying and gastrointestinal motility

Gastric emptying time in neonates, especially those less than 24 h of age, may be variable.[7] It may not reach adult levels until 6–8 months of age and may be associated with diet.[11,12] Gastrointestinal transit time may be prolonged and peristaltic activity unpredictable in young infants;[8,13] both appear affected by the feeding.[13] Lebenthal and colleagues noted that breast-fed infants, older than 45 days of age, had gastric transit times longer than 10 h while formula-fed infants had transit times less than 10 h.[14] It should also be noted that young infants have a propensity to reflux their gastric contents because of GI immaturity. All these factors affect the extent to which a drug may be absorbed.

Enzyme activity and microflora in the gastrointestinal tract

Pancreatic enzyme activity may be low at birth, but enzymes such as amylase, lipase, and trypsin develop to adult levels within the first year of life.[15] Premature infants appear to have lower amylase levels than do full-term infants. Low concentrations of pancreatic enzymes may be the reason why newborns have a decreased ability to cleave prodrug esters such as chloramphenicol palmitate.[7] Lipid-soluble drugs may not be well absorbed by neonates because of low lipase concentrations and bile acid pool.[8]

More information is needed about the microflora of the GI tract and its effect on drug absorption. In addition, the effects of various diets and antibiotic use can alter the microflora of the GI tract.[7]

Absorptive surface area

The surface area of the small intestine in young infants is proportionately greater than in adults. This physiologic difference may allow for increased drug absorption from the GI tract.

Intramuscular Absorption

When a child is unable to take a medication orally or the drug is unavailable for oral use, there may be a need to administer a drug parenterally by either the i.v. or i.m. route. Of these, the latter may be less desirable because of pain, irritation, and decreased drug delivery as compared to i.v. administration. Drug absorption after i.m. administration depends on various physicochemical and patient factors. Physicochemical factors to be considered include lipid or water solubility, drug concentration, and surface area. When addressing drug solubility, it should be noted that lipophilic drugs readily diffuse through the capillary walls of endothelial cells

whereas water-soluble drugs diffuse at fairly rapid rates from interstitial fluid to plasma via pores in capillary membranes.[16] A lipid-soluble drug may be more rapidly absorbed i.m., but a water-soluble drug may be more desirable because the drug must be stable in an aqueous solution until administered. After administration, the drug must then be water soluble at physiologic pH until absorption occurs.[16]

Drug absorption may be dependent on concentration, but available data do not allow us to determine whether an increased or decreased drug concentration results in better absorption. An increase in the osmolality of a pharmaceutical preparation secondary to the addition of another substance such as an excipient may decrease or slow down i.m. adsorption.[16] Absorption occurs more rapidly when diffusion involves a large area of muscle or the drug spreads over a large muscle mass. The massaging of an injection site after i.m. administration increases the rate of absorption.[16]

A physiologic determination of i.m. drug absorption is dependent on the adequacy of blood flow to muscle groups used for drug administration. Absorption rates differ at injection sites because blood flow varies among different muscle groups. For example, the absorption of a drug-administered i.m. in the deltoid muscle is faster than from the vastus lateralis that, in turn, is more rapid than from the gluteus.[16,17] This occurs because blood flow to the deltoid muscle is 7% higher than to vastus lateralis and 17% higher than to gluteal muscle groups.[18] Physiologic conditions that reduce blood flow to a muscle group may adversely alter the rate and/or extent of a drug-administered i.m. Decreased perfusion or hemostatic decompensation, frequently observed in ill neonates and young infants, may reduce i.m. drug absorption. Drug absorption may be adversely affected in neonates who receive a skeletal muscle-paralyzing agent such as pancuronium[16] because of decreased muscle contraction. A small muscle mass in neonates and young infants may also reduce the ability of a drug to be adequately absorbed.

The injection technique used may alter i.m. absorption. This was noted when needles of different lengths were used. The use of a longer needle (38 vs. 31 mm, 1 1/2 vs. 1 1/4 in.) for i.m. administration in adult patients resulted in higher diazepam serum concentrations.[18] This probably occurred because the drug administered with the shorter needle was actually administered s.c. rather than i.m.

Some drugs are absorbed more slowly after i.m. than oral administration; examples include diazepam, digoxin, and phenytoin. This probably occurs because these drugs require a mixture of alcohol, propylene glycol, and water for solubility, and they are insoluble in the muscle after i.m. administration.[18]

Complications associated with i.m. administration include nerve injury, muscle contracture, and abscess formation.[19] Less common problems include intramuscular hemorrhage, cellulitis, skin pigmentation, tissue necrosis, muscle atrophy, gangrene, and cyst or scar formation. In addition, injury may occur from broken needles and inadvertent injection into a joint or vein.[19]

Subcutaneous Absorption

The s.c. route is used for the administration of drugs such as insulin that require slow absorption. Injection technique and patient factors, such as fluid status and physical build, are important.[18] Exercise, elevation or warming of the injection site, or inadvertently administrating a drug i.m. rather than s.c. can increase absorption and be dangerous in some situations, such as hypoglycemia occurring in a diabetic patient from excessive insulin absorption.[18] Adverse effects that can occur secondarily to s.c. administration include tissue ischemia, sterile and nonsterile abscesses, lipodystrophy, cysts, and granulomatous formation.

Intraosseous Drug Absorption

If an i.v. line cannot be placed, the intraosseous drug administration route can be used for pediatric patients during, for example, cardiopulmonary resuscitation (CPR) because drug delivery by this route is similar to that for i.v. administration.[20] If drug or fluid delivery by this route is sluggish, a saline flush can be used to clear the needle. Intraosseous administration is used to deliver medications such as epinephrine, atropine, sodium bicarbonate, dopamine, diazepam, isoproterenol, phenytoin, phenobarbital, dexamethasone, and various antibiotics.[20]

Percutaneous or Transdermal Absorption

The percutaneous (transdermal or topical) route for systemic drug delivery is used infrequently for pediatric patients. Medications are typically applied to the skin for their local effect. In the future, this route may be used more frequently for systemic effects as more transdermal systems are developed for drug delivery.

The percutaneous absorption or the transdermal delivery of a drug occurs in the following manner. Initially a topically applied drug is absorbed into the stratum corneum and diffuses through that layer of skin into the epidermis and then into the dermis where drug

molecules reach capillaries and enter the circulatory system. Diffusion through the stratum corneum is the rate-determining step unless skin perfusion is decreased. If the latter case, diffusion is controlled by the transfer of drug molecules into capillaries rather than by the diffusion process previously explained. Percutaneous or transdermal absorption[21,22] is affected by

- Patient age.
- Application site.
- State of hydration of the stratum corneum.
- Thickness and intactness of the stratum corneum.
- Physical characteristics of the solute, and
- Physical characteristics of the vehicle or solvent.

Drug diffusion may be explained by Eq. 1:

$$J = \frac{K_m \times D_m \times C_s}{\ell} \quad (1)$$

where J is flux, K_m is the partition coefficient, D_m is the diffusion constant under specific conditions such as temperature and hydration, C_s is the concentration gradient, and l is the length or thickness of stratum corneum.[21]

Lipid-soluble drugs are better absorbed into the stratum corneum than are water-soluble drugs, but the latter do not easily traverse the stratum corneum. Thus, lipid-soluble drugs are more likely to be stored in the stratum corneum, whereas water-soluble drugs are more likely to diffuse across the stratum corneum to the epidermis and dermis.[21]

Patient age

Drug absorption transdermally is not appreciably different in various age groups of patients except for neonates less than 32-week gestation at birth.[23] Drug absorption is increased in premature neonates, because the stratum corneum is not completely formed at birth. An example of increased drug absorption occurred in two premature neonates who were repeatedly washed with 3% hexachlorophene and developed encephalopathy secondary to drug absorption.[21] The absorption of the corticosteroid betamethasone valerate after topical application in children resulted in hypothalamus-pituitary-adrenal axis suppression. Children may have increased drug absorption from the percutaneous application of drugs not because of higher absorption rate but because of a greater topical application or a larger dose per kilogram. Examples of deaths in children from percutaneous drug absorption include those caused by salicylic acid and phenol absorption.[21] Toxicity has also been noted with the topical application of iodine and alcohol-containing products.[23]

Application site

The ability of a drug to be absorbed transdermally depends on the thickness of the stratum corneum. For example, absorption occurs more readily through abdominal skin than through skin on the plantar surface of the foot. Topical absorption may be enhanced from a particular site by the application of an occlusive dressing.

Status of the stratum corneum

Percutaneous absorption of a drug is enhanced by the hydration of the stratum corneum. Such hydration affects the absorption of hydrophilic drugs more than lipophilic drugs. Drugs will penetrate damaged skin more than intact skin. Skin damaged because of dryness will allow for increased drug penetration through areas where the skin is cracked or broken.

Solute

The penetration of the solute (or drug) depends on its polarity and on the polarity of the delivery vehicle.

Vehicle or solvent

Drug-delivery vehicles typically used for topical application include lotions, ointments, creams, emulsions, and gels. Substances such as emulsifiers may be added to the drug and vehicle to improve the texture of an emulsion, a stabilizer to preserve drug stability, the vehicle, or both, a thickening agent to increase viscosity, or a humectant to draw moisture into the skin.[21] It is particularly important to consider the vehicle and other additives when selecting a topical drug preparation for a neonate, especially when premature, because of the greater possibility of absorption of not only the drug but also other product ingredients. Toxic reactions have occurred in neonates from ingredients considered "inactive."

Transdermal Drug-Delivery Systems

Drugs chosen for delivery via a transdermal drug-delivery system must adequately penetrate the skin in such a way that the system determines the delivery rate that should be fairly constant.[21] In addition, the drug must not irritate or

sensitize the skin. It is hoped that in the future more drugs will be developed for transdermal delivery. This could become an alternative route for drug delivery to children who have difficulty with oral administration.

Endotracheal Absorption

The endotracheal (ET) route has been used to administer medications during CPR when other routes, such as the i.v. route, are unavailable. It provides rapid access as well as rapid drug absorption and distribution.[24] Some studies have shown that the time to reach peak absorption is similar to that for the i.v. route, but serum concentrations achieved were 10–33% of that achieved with i.v. administration, resulting in a weaker response. A depot effect has also been demonstrated for drugs such as epinephrine. Work needs to be done to determine the optimal dose by this route, drug-delivery vehicle, and the most effective delivery technique.

Rectal Absorption

The rectal route is used for local and systemic therapy for the following reasons:[25]

- Nausea or vomiting.
- Rejection of oral administration because of its taste, texture, etc.
- Upper GI disease that might affect absorption.
- Medication absorption affected by food or gastric emptying.
- Medication is readily decomposed in gastric fluid but may be stable in rectal fluid, and
- First-pass effect of high-clearance drug may be partially avoided.

Absorption from the rectum depends on various physiological factors such as surface area, blood supply, pH, fluid volume, and possible metabolism by microorganisms in the rectum. The rectum is perfused by the inferior and middle rectal arteries, whereas the superior, the middle, and the inferior rectal veins drain the rectum.[25] The latter two are directly connected to the systemic circulation; the superior rectal vein drains into the portal system. Drugs absorbed from the lower rectum are carried directly into the systemic circulation, whereas drugs absorbed from the upper rectum are subjected to hepatic first-pass effect.[25] Therefore, a high-clearance drug should be more bioavailable after rectal than oral administration. The volume of fluid in the rectum, the pH of that fluid, and the presence of stool in the rectal vault may affect drug absorption. Because the fluid volume is usually low compared to that in other areas of the GI tract, a drug may not be completely soluble. In addition, a variety of organisms colonize the rectum, and it is debated whether these organisms are involved in drug metabolism.[25] Absorption is also influenced by the dosage form used. For example, drugs are rapidly absorbed rectally from aqueous or alcoholic solutions, whereas absorption from a suppository depends on its base, the presence of a surfactant, particle size of the active ingredient(s), and drug concentration.[25] The following problems may be associated with the rectal route for drug administration:[25]

- Decreased absorption secondary to defecation of the rectally administered pharmaceutical product.
- Less adsorption rectally than orally because the absorbing surface area of the rectum is smaller.
- Dissolution problems for rectally administered medications because of lower fluid volume in the rectum than in the stomach, duodenum, etc.
- Microorganisms in rectum may cause degradation of some medications.
- Patient or parent acceptance.

Distribution

A drug is distributed by moving from a patient's systemic circulation to various compartments, tissues, and cells. Distribution depends on patient factors, drug physiochemical properties, and the route of drug administration. Patient factors that influence drug distribution or the volume of drug distribution (V_d) include body composition, perfusion, protein- and tissue-binding characteristics, and permeability.[7,8] Many of these characteristics are age dependent. Drug physiochemical properties that may influence distribution include molecular weight, pK_a, and partition coefficient.

Differences in body composition

Age-related changes in body composition can alter the V_d of a drug. At birth, 85% of the weight of a premature infant may be water, compared to approximately 75% as total body water (TBW) in a full-term infant.[13] Neonates have the highest percentage of extracellular water (65% of TBW in premature infants as compared to 35–44% in full-term neonates and 20% in adults). The intracellular water (ICW) is more stable throughout life (i.e., 25% in premature neonates, 33% in full-term neonates, and 40% in adults).[7] An infant's percentage of TBW approaches that of an adult male by 1 year of age (60% TBW); it reaches the same about the time of puberty or 12 years of age.[8] Women have a lower percentage of TBW (50%)

than men do because they have a higher concentration of body fat. Thus, neonates, because of their high TBW, have a higher V_d for water-soluble drugs such as aminoglycosides than older children or adults. For example, the V_d for an aminoglycoside such as gentamicin approximates that of extracellular cellular fluid volume, 0.5–1.2 L/kg for a neonate, but only 0.2–0.3 L/kg for an older child or an adult.[8]

Adipose tissue increases from as little as 0.5% in a premature infant to approximately 16% of body weight for a full-term infant.[26,27] Boys experience a spurt in body fat between the ages of 5 and 10 years, and then a gradual decrease in fat content until about 17 years of age; girls usually have a rapid increase in adipose tissue at puberty.[9] Thus, one would expect neonates and young infants to have a decreased V_d for lipid-soluble drugs. This has been noted for diazepam in neonates who have exhibited an apparent V_d of 1.4–1.8 L/kg compared to 2.2–2.6 L/kg in adults.[28]

Protein binding

Neonates have lower concentrations of various plasma proteins (e.g., albumin concentrations about 80% of those in adults) for drug binding, but the albumin present may also have a lower affinity for binding drugs than noted for adults who are receiving the same medications. This lower affinity for binding drugs may result in a competition for various albumin-binding sites with substances such as bilirubin. Plasma protein binding noted in adults is usually achieved in children by the age of 1 year.[13]

In neonates drugs such as various penicillins, phenobarbital, phenytoin, and theophylline have lower protein-binding affinity than in adults. This may increase the concentration of free or pharmacological active drug in neonates, and may also change the apparent volume of distribution. Thus, neonates may require different doses on a mg/kg basis compared to that for adults for these drugs to achieve appropriate therapeutic serum concentrations.

In addition to binding to plasma proteins in the neonate, some drugs such as sulfonamides may displace plasma bilirubin from binding sites. This may increase an infant's risk for developing kernicterus. The significance of drugs displacing bilirubin is controversial because bilirubin may have a greater affinity for albumin than drugs have.[29]

Tissue binding

The binding of drugs to various body tissues appears to vary with age; for example, digoxin binding to erythrocytes is higher in neonates than in adults. This may be due to the increased number of binding sties on neonatal erythrocytes.[30]

Drug penetration into the central nervous system

A drug is more likely to cross into the central nervous system (CNS) of a neonate rather than an older child or an adult. This most likely occurs because its CNS is less mature and the blood-brain barrier is less formed. This is an important consideration when antimicrobial therapy is needed for the treatment of bacterial meningitis or anticonvulsant for seizures.

Metabolism

Although drug metabolism can occur in various body organs including the lungs, GI tract, liver, and kidneys as well as in the blood, the liver is the primary organ for metabolism. Most drugs are metabolized from lipid-soluble parent compounds to more polar, less lipophilic metabolites that are more readily eliminated renally.[9]

Hepatic metabolism

Most drug metabolism occurs in the liver by phase I or phase II metabolic processes. Phase I reactions primarily biotransform an active drug to a more water-soluble compound that typically is inactive or has less activity than the parent compound. Oxidation, reduction, hydralysis, and hydroxylation are examples of phase I reactions.[6,8,16] Oxidation is primarily catalyzed by the cytochrome (CYP) P450 system that has a multitude of isozymes (at least 13 primary enzymes) with a multitude of isozymes of specific gene families.[6] It appears that isozymes CYP450 1A2, 2D6, 2C19, and 3A3/4 are involved in drug metabolism in humans.[6] Oxidizing enzyme systems appear to mature after birth so that by the age of 6 months, activity is similar to or even exceeds adult levels. More information about drugs affected by phase I reactions may be found in Ref. [6].

Phase II reactions (glucuronidation, sulfation, acetylation, and glutathione conjugation) usually involve the conjugation of active drugs with endogenous molecules to form metabolites that are more water soluble;[16] glucuronidation is the most thoroughly studied reaction. It is postulated that maternal glucocorticoids inhibit the development of glucuronyltransferase, the enzyme involved in glucuronidation in utero. After birth this metabolic system matures rapidly and reaches adult levels by the age of 2 years.[29]

Sulfate conjugation appears to be fully developed immediately prior to or at the time of birth. Infants and

young children readily sulfate acetaminophen; in adults the major metabolic route is glucuronidation.[31] Little is known about acetylation in neonates or infants. It is believed that neonates have an extremely low capacity for acetylation at birth, but this pathway matures at approximately 20 days of age.[29]

Theophylline is an example of a drug that is readily metabolized in neonates by N-methylation to caffeine (process not relevant clinically in older infants, children, and adults). It is also a compound that has pharmacologic activity versus apnea (like theophylline), but which may have toxicity when it is not readily metabolized by the liver, and its elimination is slowed by immature kidneys.[6]

Neonates require close monitoring if their mothers received enzyme inducers such as phenytoin, phenobarbital, carbamazepine, or rifampin during pregnancy or if they need one of these drugs themselves.[16] Examples of drugs that inhibit the metabolism of other medications include cimetidine, erythromycin, and ketoconazole.[16]

Renal Elimination

The kidneys are the major route for drug elimination, especially for water-soluble compounds or the metabolites of lipid-soluble drugs. Renal drug elimination is dependent on renal blood flow, glomerular filtration, and tubular secretion and reabsorption. These functions appear to mature at different rates in the neonate and infant. Full-term infants achieve renal blood flow similar to that of adults by the age of 5–12 months; glomerular filtration approaches adult values by the age of 3–5 months.[6] Premature neonates exhibit lower rates for glomerular filtration at birth than do full-term neonates, and more time is required of them postnatally to develop filtration ability.[32] This is probably due to their lack of as many functional nephrons at birth. Tubular function is less mature in the neonate at birth than is glomerular filtration, and it matures at a slower rate. Tubular function begins to approach adult values by 7 months of age. Renal function is equal to that of adults by 1 year of age.

Aminoglycosides (e.g., gentamicin, tobramycin, amikacin) and digoxin are drugs whose eliminations are affected by renal maturation. The renal elimination of aminoglycosides in neonates and young infants parallels the maturation of glomerular function and correlates with creatinine clearance.[33] The renal elimination of digoxin parallels kidney maturation. Dosage adjustment for this drug is necessary as renal function matures in neonates and young infants. In addition, older infants and children require higher mg/kg doses of digoxin than do adults to achieve the same serum concentrations. This may be due to decreased digoxin absorption or increased renal elimination.[8]

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring should encompass the entire drug-use process including drug selection, product selection, administration route, patient age, appropriate dosing on a mg/kg or mg/m^2 basis, and monitoring serum concentrations when appropriate and observing the patient for optimal drug effect(s) and possible adverse drug events.

Important Differences in Pediatric Serum Drug Concentrations

For many drugs, especially for those with narrow therapeutic indexes, serum concentration ranges have been determined that correlate to minimum and maximum therapeutic effects as well as to the development of toxicity. Therapeutic serum concentration ranges for various drugs have been developed for adults, and these data have been applied to pediatric patients including neonates. Such data may be appropriate to monitor drug therapy in children, but possibly not in children of all ages or possibly not in children at all. For example, Painter et al.[34] noted that neonates need higher serum phenobarbital concentrations than do older children and adults to terminate seizures. Gilman et al.[35] observed that higher phenobarbital loading doses were needed to achieve serum concentrations in neonates that would reduce the occurrence of seizures. Thus, there may be a need for different serum concentration ranges for various drugs needed by different age groups of patients for a similar pharmacodynamic or therapeutic outcome.

Free serum concentrations, rather than total concentrations, of some drugs such as phenytoin may need to be monitored in some patients, including neonates, who have low serum albumin. Gilman has advocated the possibility of using individualized dosing and serum concentration range for pediatric patients because children, especially neonates, have rapidly maturing functions of various organs and changes in albumin for drug binding.[36]

Serum concentration monitoring of various drugs administered to pediatric patients may appropriately give information about the drug but not its metabolites. This may be a problem when children metabolize specific drugs differently than adults with resulting differences in metabolite concentrations or the presence of different metabolites. This has been noted when premature infants

have been administered theophylline for central apnea. A major metabolite of theophylline in neonates is caffeine, although only small concentrations of this metabolite are noted in older children and adults.[37,38] Caffeine is effective in treating apnea, and thus may add to the effectiveness of theophylline. This may help explain why lower theophylline serum concentrations may be needed for apnea rather than asthma. In addition, the presence of the 4-en metabolite of valproic acid noted in the serum of infants and young children, but not adults, receiving this medication for seizures may be responsible for the hepatoxicity of this drug in young pediatric patients.[36,39]

Serum Drug Concentrations

Because of the cost associated with therapeutic drug monitoring, serum drug concentrations must be drawn appropriately to provide useful information. Drugs typically followed pharmacokinetically are those with narrow therapeutic indexes for which there is an association between pharmacokinetic and pharmacodynamic data or toxicity. For many drugs, especially for those administered orally, the determination of trough concentrations (serum concentrations obtained prior to administration) may be most appropriate. This eliminates differences in absorption rates that could influence peak concentrations (e.g., orally administered phenobarbital, phenytoin, carbamazepine, or valproic acid). Trough concentrations may be important for drugs such as digoxin that take time to distribute to tissue receptors in such a way that serum concentrations reflect pharmacodynamic effects. Peak concentrations are best used for determining toxicity and therapeutic effects of drugs with short half-lives.

Table 2 gives therapeutic serum concentrations and pharmacokinetic information for some drugs administered to pediatric patients.

Technical Factors

Sample size and timing of blood drawing for serum concentration determination

Because of the small blood volume and the small size of veins, it is technically difficult to draw blood from neonates, infants, and young children for therapeutic drug monitoring, and it is therefore important to determine the best drawing schedule. For example, when are peak and trough data needed compared to trough data only? For anticonvulsants administered orally or i.v., trough concentrations are needed, whereas for aminoglycosides it may be important to obtain both peaks and troughs.

DOSING REGIMENS

Drugs for pediatric patients should be dosed on a mg/kg or a mg/m^2 basis using information available for the patient's age group. In addition, the patient's renal and hepatic functions must be considered. The route for administration must be determined based on the severity of the illness, the availability of the medication for a particular route of administration, and whether the patient is able to take a medication orally.

The Bibliography succeeding the References at the end of this chapter contains a list of handbooks and other references that are useful sources of dosing information for neonatal and/or pediatric pediatrics. In addition, drug information centers in pediatric hospitals or university settings are another excellent resource for pediatric drug information.

EXCIPIENTS OR ADDITIVES IN MEDICATIONS

Pharmaceutical products may contain, in addition to the active or therapeutic agent(s), a variety of other ingredients that are termed inactive or inert that are categorized as excipients or additives (flavorings, sweeteners, preservatives, stabilizers, diluents, lubricants, etc.). The words inert or inactive are misnomers for some excipients because some have been shown to cause adverse effects. Neonates and young children are at risk for such adverse effects, because they may not be able to metabolize or eliminate an ingredient in a pharmaceutical product in the same manner as an adult. In addition, patients of various ages have experienced allergic reactions to excipients such as tartrazine dyes.

Benzyl alcohol is a preservative that may be present in multidose vials of bacteriostatic sodium chloride and bacteriostatic water for injection and pharmaceuticals available in multidose vials for parenteral use. An association between the presence of benzyl alcohol in solutions used for flushing intravascular catheters and to reconstitute medications and a gasping syndrome and deaths in neonates was first reported in the early 1980s.[40,41] The neonates also displayed clinical findings such as an elevated anion gap, metabolic acidosis, CNS depression, seizures, respiratory failure, renal and hepatic failures, cardiovascular collapse, and death. Those at highest risk were premature infants who weighted less

Table 2 Pediatric pharmacokinetic data of some medications[a]

Drug	Therapeutic serum concentration (μg/ml)	Bioavailability (for oral drugs) (%)	Plasma protein binding (%)	V_d (L/kg)	$t_{1/2}$ (h)
Carbamazepine	4–12	>70	40–90	1.5 (neonate) 0.8–1.9 (child)	8–25 (child) $t_{1/2}$ varies with multiple dosing
Clonazepam	20–80 ng/mL	>85	47–80	3.2 (child)	20–40 (child)
Ethosuximide	40–100	~100	0	0.6–0.7 (child)	24–36 (child)
Gentamicin	trough ≤2 peak 4–10	Not available	<30	0.4–0.6 (neonate) 0.3–0.35 (child)	3–11.5 (<1 wk) 3–6 (1 wk-6 mo) 1.2 (child)
Phenobarbital	15–40	80–100	40–60	0.6–1.2 (neonate) 0.7–1 (child)	45–173 (neonate) 37–72 (child)
Phenytoin	10–20	85–95	>90	1–1.2 (premature neonate) 0.8–0.9 (full-term neonate) 0.7–0.8 (child)	6–140 (<8 days)[b] 5–80 (9–21 days)[b] 2–20 (21–36 days)[b] 5–18 (child)[b]
Theophylline	5–15	Up to 100%, depending on the formulation	32–40 (neonate) 55–60 (child)	0.4–1 (premature neonate) 0.3–0.7 (child)	19.9–35 (neonate) 3.4 ± 1.1 (1–4 yrs)
Valproic acid	40–100 (150)[c]	100	>90[d]	0.2 (child)	23–35 (neonate) 4–14 (child)

[a]Age or stage of life in parentheses.
[b]Michaelis–Menton pharmacokinetics; $T_{1/2}$ varies with serum concentration.
[c]Upper end of the serum concentration range is not definitely established.
[d]May vary with serum concentration.
(Adapted from Sagraves, R. Epilepsy and other Convulsive Disorders. *In Pediatric Pharmacotherapy*, 2nd Ed.: Kuhn, R.J. (Ed.) University of Kentucky: Lexington, 1993; Taketomo, C.K.; Hodding, J.H.; Kraus, D.M. *Pediatric Dosage Handbook*; LEXI-COMP, Inc.: Hudson, OH, 2000; Kauffman, R.E. Drug Therapeutics in the Infant and Child. In *Pediatric Pharmacology: Therapeutic Principles in Practice*. Yaffe, S.J.; Aranda, J.V., (Eds.); W.B. Saunders Co.: Philadelphia, 1992, 212–219; A. Rane, Drug Disposition and Action in Infants and Children. In *Pediatric Pharmacology: Therapeutic Principles in Practice*. Yaffe, S.J.; Aranda, J.V.; (Eds.); W.B. Saunders Co.: Philadelphia, 1992, 10–19.)

than 1250 g at birth.[40–42] In a study by Benda et al., premature neonates who survived benzyl alcohol administration were compared to neonates born after the use of benzyl alcohol-containing flush solutions was discontinued.[43] They noted that survivors had a higher incidence of cerebral palsy (50%) compared to infants who did not receive benzyl alcohol flushes (2.4%) ($P < 0.001$). In addition, the incidence of cerebral palsy and developmental delay was 53.9% versus 11.9% in the two populations ($P < 0.001$). The cause is probably associated with benzyl alcohol use and the inability of neonates, especially those who are premature, to adequately metabolize benzyl alcohol.[44] The American Academy of Pediatrics,[45] the Centers for Disease Control,[46] and the FDA[47] recommend that the administration of products containing benzyl alcohol be avoided in infants. Preservative-free i.v. flush solutions are recommended.[45–47]

Initially, it was believed that benzyl alcohol was only toxic in neonates who received doses greater than 99 mg/kg,[42] but it has been suggested that lower doses may be toxic, resulting in kernicterus and intraventricular hemorrhages.[48,49] Therefore, pharmaceutical preparations and fluids containing benzyl alcohol should be avoided in premature neonates.

Benzoic acid and sodium benzoate are added in low concentrations to various pharmaceutical preparations as bacteriostatic and fungistatic agents. Hypersensitivity reactions to benzoates have occurred when administered to allergic patients, such as those with asthma, those who do not tolerate aspirin, and those with a history of urticaria.[44] Hyperbilirubinemia and systemic effects attributed to benzyl alcohol may occur in premature neonates because benzyl alcohol is metabolized to benzoic acid.[44]

Propylene glycol is found as a solvent in some i.v. multiple vitamin preparations and a variety of pharmaceutical preparations for parenteral administration including phenytoin, digoxin, and diazepam. MacDonald et al.[50] noted that neonates who received MVI-12 (propylene glycol dose of approximately 3 g/day) versus those who received MVI concentrate (propylene glycol dose of approximately 300 mg/day) had a significant increase in seizures. In addition, infants in the first group suffered from hyperbilirubinemia and renal failure. (Although MVI concentrate is no longer on the market in the United States, it was used in the early 1980s.)

Serum hyperosmolality has been reported in infants who received vitamin preparations,[51] and in burn patients due to the topical absorption of propylene glycol-containing products.[52,53] In addition, burn patients have experienced metabolic acidosis with a high anion gap, decreased ionized calcium concentrations, acute renal failure, and death from topical propylene glycol absorption.[44,54] Problems associated with the oral ingestion of propylene glycol-containing products by children include CNS depression, seizures, and cardiac dysrhythmias.[55] Hypotension, cardiac dysrythmias, respiratory depression, and seizures have occurred after the rapid administration of phenytoin that may be associated with the propylene glycol.[56]

The American Academy of Pediatrics Committee on Drugs recommends that medications intended for pediatric use be ethanol free.[57] If, because of stability or solubility problems with the active ingredients(s), liquid medications need ethanol as an ingredient, but they should not contain more than 5% v/v ethanol.[57] The Academy also recommends that the ingestion of a single dose of an ethanol-containing product by a pediatric patient should not result in blood ethanol concentrations greater than 25 mg/100 mL, the volume of a packaged liquid medication should be of a minimal amount so that its entire ingestion would not result in a lethal dose and safety closures should be on all medicinals containing greater than 5% v/v ethanol. In addition, the Academy suggests that children under 6 years of age who need an ethanol-containing OTC preparation be under medical supervision and that doses of any ethanol-containing product be spaced at intervals to avoid ethanol accumulation.[57]

The Academy of Pediatrics made their recommendations concerning ethanol exposure from medications based on potential acute and chronic ethanol-related problems. Acutely, the coadministration of ethanol may alter drug adsorption or metabolism, and may result in drug interactions (e.g., increased sedation when taken with sedatives). Disulfiram-like reactions have occurred after the ingestion of an alcohol-containing medication or when an ethanol-containing product is used in conjunction with medications such as metronidazole, sulfonamides, or chloramphenicol.[57] The CNS effects (muscle incoordination, a longer reaction time, behavioral changes) are the most commonly reported acute adverse reactions associated with ethanol ingestion. Such reactions have occurred with blood ethanol concentrations in the range of 1–100 mg/100 ml.[57] Lethal ethanol doses in children occur at approximately 3 gm/kg although deaths due to ethanol-induced hypoglycemia have occurred at lower doses or because of interactions with other medications.[57,58] Chronic ethanol exposure may induce hepatic enzymes, and may thus alter the clearance of drugs such as phenytoin, phenobarbital, and warfarin.[59] Examples of other additives that have been problematic in pediatric patients include lactose,[55] tartrazine dyes[44,55] and sulfites.[55]

It is therefore important for health care professionals, and especially those who are responsible for selecting and administering medications to premature neonates, to examine pharmaceutical preparations for the presence of inactive ingredients as well as for the active drug. The provision of medications should be based on choosing the safest preparations possible. Various brands of medications should be compared to ensure that products without hazardous excipients. In the hospital setting, pharmacy and therapeutics committees and the pharmacy department play important roles in this process because they compare pharmaceutical preparations for formulary selection. In the outpatient setting, physicians and pharmacists must responsibly select the most appropriate brand of a particular medication. Kumar et al.[60] recommend that labeling for pharmaceutical products should include the names and the amounts of excipients as well as active ingredients to help health care professionals select appropriate drug products for neonates.

INTRAVENOUS ADMINISTRATION

Without being properly instructed about methods used for administering i.v. medications to pediatric patients, health care personnel may give a medication incorrectly, resulting in an inappropriate or unexpected therapeutic response. Therefore, it is important that health care personnel (nurses, physicians, pharmacists) understand how medications are administered by this route.

The i.v. route is most frequently chosen for medication delivery when a patient's clinical condition requires that a medication be administered by the most expeditious and complete method possible. In addition, some drugs are

only available for i.v. administration. Although this route is the most reliable for drug delivery to the systemic circulation, problems can occur that reduce and/or delay medication delivery because of the product selected, dosage volume needed, or frequency of administration, but problems can also be associated with the i.v. delivery system used. The latter occur most frequently when a small medication volume is administered at a slow rate as is often needed for a neonate or young infant. A brief discussion of problems associated with i.v. drug delivery to pediatric patients is given here. A thorough overview of i.v. drug administration to pediatric patients is provided in Refs. [61] and [62].

Disposable IV Equipment, Effects on Drug Delivery

Infusion rates and location of injection sites

The first article to explore problems that can occur with i.v. drug delivery to pediatric patients was published in 1979 by Gould and Roberts.[63] They demonstrated in their study using an in vitro system for drug administration (Fig. 1) that infusion rates as well as the location of the injection sites in the i.v. infusion system influence the infusion profile of i.v. administered medications. Fig. 1 shows the effects of different i.v. fluid rates on the length of time to infuse 95% of a gentamicin dose administered at various sites in the infusion system.[63] It was reported that at a slow infusion rate of 3 ml/h, a drug takes longer to be infused and that the time for infusion time depends on the site of administration (i.e., the further the drug injection from a patient, the longer to administer 95% of the medication, see Fig. 2). Thus, it took approximately 400 min to infuse gentamicin at an infusion rate of 3 ml/h via a Y-site in the administration system. However, the same drug administered at a butterfly injection site at the same fluid flow rate reduced the length of time to administer 95% of the drug to less than 20 min. Gould and Roberts also stated that the time needed for drug administration in their i.v. system was longer than what had been expected.[63]

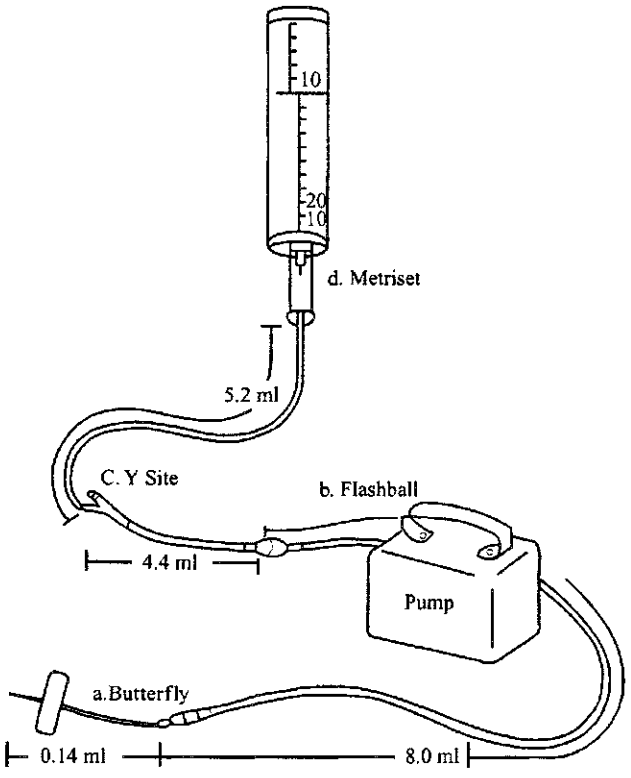

Fig. 1 Intravenous administration system used by Gould and Roberts. (From Ref. [63].)

Type of injection site

Leff and Roberts[61] demonstrated that the amount of drug received by a pediatric patient and the drug-delivery rate are influenced by the type of injection site (Y-site, T-type, T-connector, stopcock, etc.) and the volume (dead space) contained in the particular site. For the delivery of small dosage volumes (less than 1 ml) i.v. tubing should have microinjection sites that prevent a drug from being sequestered in the injection site. In addition, the amount of i.v. fluid needed to adequately flush microinjection sites to clear the medication would be less than needed to flush injection sites found on tubing used to administer drugs to adults.

Fluid flow dynamics

Another characteristic of i.v. tubing that affects drug delivery is fluid flow dynamics. It appears that flow in i.v. tubing is best characterized by laminar flow, and the radius of the tubing. Poiseuille's law describes flow in i.v. tubing as

$$\frac{q_v = Pr^4}{4nL} \tag{2}$$

where q_v is the volumetric flow rate, P is the pressure change in the i.v. tubing, r is the radius of the i.v. tubing, n is the viscosity of the fluid, and L is the length of the i.v. tubing.

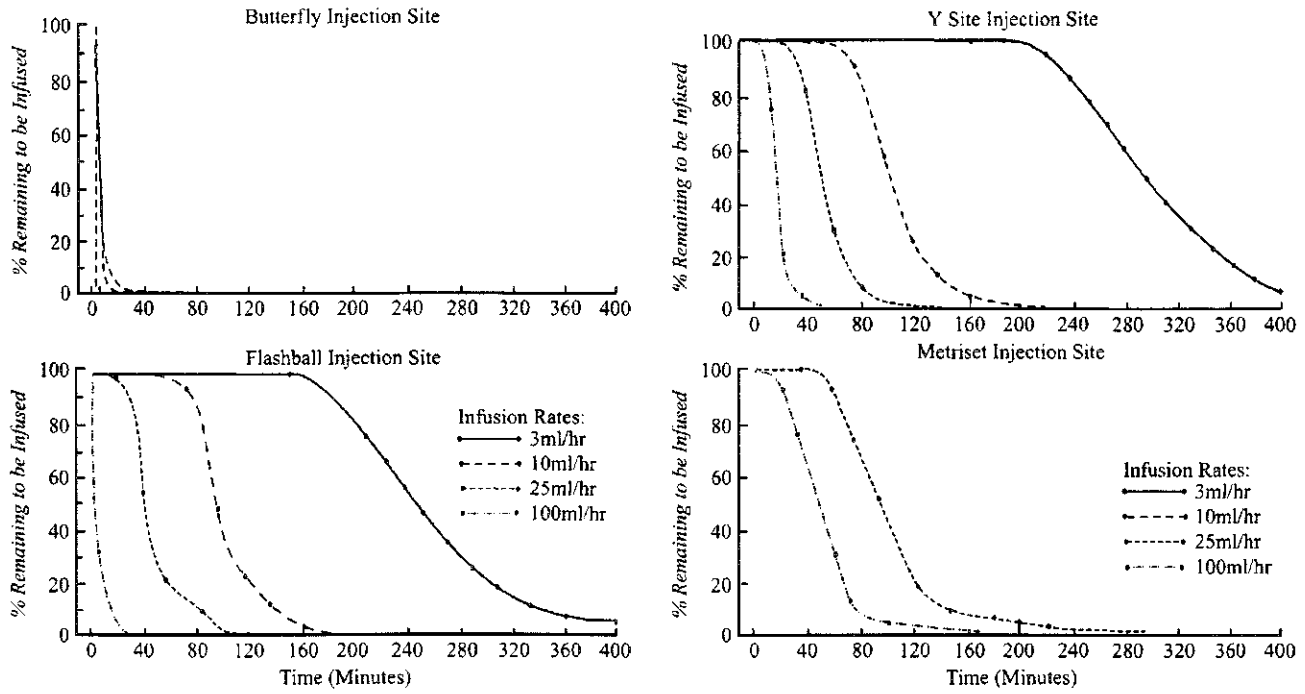

Fig. 2 Influence of i.v. flow rate on the infusion profile of gentamicin. (From Ref. [61].)

Thus, for i.v. delivery to pediatric patients, microbore tubing with an intraluminal diameter of <0.06 in. should be used rather than macrobore tubing. The use of microbore tubing allows the use of longer tubing lengths without significantly increasing delivery time.

Filters

A filter, especially one with a large reservoir volume, may prolong and/or reduce drug delivery. This occurs if the drug and its diluent are of different densities and there is a layering out of the drug in the filter.[64] Therefore, a filter with a smaller reservoir volume should be selected.

Drug and Fluid Considerations for Intravenous Drug Administration

Characteristics of the drug and the fluid such as drug volume, osmolality, pH, and density may affect i.v. drug delivery. The frequency and duration of drug administration is also important as is the need for the infusion system to handle multiple drugs. This may lead to drug incompatibilities and problems in medication scheduling.

Osmolality and pH

Osmolality and pH must be considered when preparing a drug solution for i.v. administration to pediatric patients. Problems such as tissue irritation, pain on injection, phlebitis, electrolyte shifts, and even intraventricular hemorrhages in neonates have been associated with the administration of drug solutions with high osmolalities.[65] Drug solutions should have osmolalities similar to serum osmolality, if possible. To control the osmolality, a drug can be diluted with a vehicle selected for i.v. infusion via a syringe infusion system[65] or the i.v. flow rate can be adjusted to achieve a particular drug-vehicle osmolality.[61]

Density

If the density of a drug is significantly different from that of the diluent, the drug may layer out on the filter or in the i.v. tubing. The latter occurs more frequently if macrobore tubing, a low flow rate, the i.v. system, or if the tubing is in a particular position. A density problem can be avoided by using microbore tubing which promotes mixing; this is especially important when i.v. flow rates are low, as are needed for neonates or young infants.

Frequency and Duration of Drug Administration; Multiple Drugs

To ensure that frequent doses are administered at appropriate intervals or that multiple drugs are administered to avoid drug incompatibilities, a syringe infusion pump can be used to administer drug volumes over a specific length of time. This helps avoid a situation where part of a drug dose is left in the tubing when the i.v. set is changed, as has been reported for manual administration techniques. More than one syringe pump can be used to simultaneously administer compatible drugs in a parallel system into a micro-Y-site or stopcock.

Types of Intravenous Administration

Drugs may require i.v. administration as continuous infusions or at intervals (q4h, q6h, q12h, etc.). Manual methods require the administration of the drug into the i.v. system at an injection site (Y-site, T-connector, stopcock, etc.), added to the i.v. solution in a mixing chamber, or added to an i.v. bag to be administered via gravity. A syringe pump or another mechanical device may be used for drug administration.

Manual administration

Manual administration is not as accurate as using a syringe pump for drug administration. It has been used for small volumes of medication (<3 ml), a low flow rate (<20 ml/h), or if the antegrade (forward toward the patient) injection of a drug bolus is safe.[61] If a medication is to be administered antegrade, it should be administered slowly into a microinjection site toward the patient; microbore tubing should be placed between the injection site and the patient to reduce the time to get the drug to the patient. Leff and Roberts[61] recommended that the volume of the drug to be injected by the antegrade technique should be a smaller volume than the tubing fluid volume between the injection site and the patient. If the medication volume is too large to be safely given by antegrade administration, but the i.v. fluid flow rate is low (< 20 ml/h), the drug may be administered by a retrograde technique (Fig. 3).

Mechanical system for drug administration

If a mechanical system is chosen for drug administration, the appropriate infusion device must be selected based on its operating mechanism, flow accuracy, flow continuity,

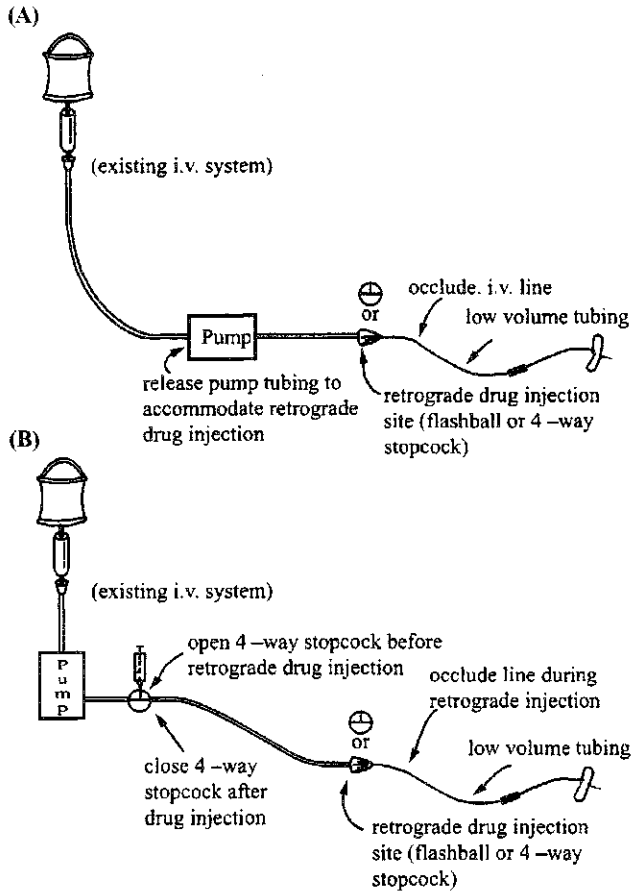

Fig. 3 Examples of retrograde system setups. (From Leff, R.D.; Roberts, R.J. Methods for intravenous drug administration in the pediatric patient. J. Pediatr. 1981, *98*, 631–635.)

and ability to detect occlusions. Other important factors include an alarm system, ease of operation, ability to be cleaned easily, and safety from children inadvertently trying to change pump settings. A syringe pump is best for delivering small dosage volumes and when intermittent intervals are needed for medications. It is the mechanical device most often selected for medication administration because it can be used for intermittent administration of small and large doses, or for the continuous infusion of medications at low rates. A drug can be administered separately from the primary i.v. fluid flow rate, with the drug and the fluid mixing for a short distance therefore in microbore tubing (see Fig. 4) before reaching the patient. In addition to being able to more accurately deliver medications than by manual methods, syringe pump systems have the advantage of being able to separate the administration of incompatible drugs, reduce difficulties associated with the administration of

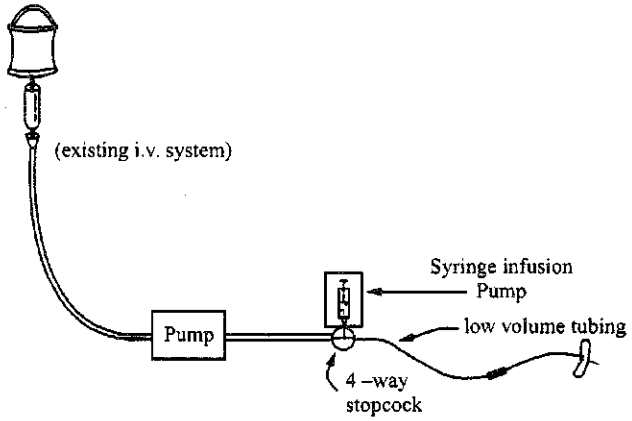

Fig. 4 Syringe pump setup with drug administered separately of the primary i.v. fluid flow rate. Mixing of the drug and i.v. fluid occurs at a stopcock and for a short distance in microbore tubing. (From Leff, R.D.; Roberts, R.J. Methods for intravenous drug administration in the pediatric patient. J. Pediatr. 1981, *98*, 631–635.)

multiple doses, and shorten the time required to administer medications.

Additional Comments About IV Drug Administration

Reed and Gal[6] recommended the following steps to decrease problems associated with i.v. drug administration to pediatric patients:

1. Standardize and document total time for drug administration.
2. Document the volume of any solution used to flush an i.v. dose.
3. Standardize infusion techniques for drug administration, especially for those with a narrow therapeutic index.
4. Use the largest gauge cannula that can be used.
5. Standardize dilution and infusion volumes for drugs given by intermittent i.v. injection, and avoid attaching lines for drug infusion to a central hub with solutions infused at widely disparate rates, and
6. Use low-volume i.v. tubing and use the most distal sites for drug administration.

In addition, one must remember that for infants the amount of fluid required for drug administration may take away from the amount of fluid available for nutrition. Thus, with medication administration, the fluid volume must be as restrictive as possible so that the bulk of the daily fluid intake can be saved for nutrition. Health care providers must closely monitor daily fluid intake from all sources to prevent fluid overload and must also watch the osmolality of medications with diluents.

ADMINISTRATION OF ORAL MEDICATIONS

The oral route is typically the preferred route for medication administration to pediatric patients. Other routes may be used, if the patient cannot take a medication orally because of vomiting, being unable to swallow, or the medication is unavailable for oral use. In addition, for specific problems it may be better to deliver the medication directly to the area being treated, for example, inhalation, ophthalmic administration, or otic administration.

Dosage Forms

Oral liquids

Liquid medications are the most commonly administered oral medications to pediatric patients because of the ease of swallowing by infants and young children who cannot swallow solid dosage forms. However, availability of some medications as liquid formulations may be limited. If not available in liquid form, a solid dosage form may need to be modified by the pharmacist, other health care provider, or by the parent. If a solid dosage form is modified, for example a suspension is prepared, will the drug be stable and for how long, and will it be absorbed differently than the original dosage form? These are just a few questions that must be answered about the extemporaneous preparation of a drug product for a pediatric patient.

Alcohol-free products should be selected for pediatric patients whenever possible. Furthermore, the inactive ingredients or excipients contained in an oral preparation should be identified. This is especially important if the patient is known to have had an adverse reaction to a particular excipient or there is another reason to avoid a particular additive in a medication. The Committee on Drugs of the American Academy of Pediatrics recommended that pharmaceutical products contain a qualitative listing of inactive ingredients in order that products containing these substance could be avoided in patients who had problems with specific adjuvants.[55] Kumar et al.[60] contains lists of inactive ingredients (sweeteners, flavorings, dyes, and preservatives) found in many liquid medications such as analgesics, antipyretics, antihistamine decongestants, cough and cold remedies, antidiarrheal agents, and theophylline preparations. The authors of the

Table 3 Osmolalities of liquid pharmaceuticals for oral administration

Liquid preparation	Osmolality (mean ± sEM)
Propylene glycol	8326 ± 1467
Saccharin-containing drugs	
Albuterol	65
Haloperidol	47
Suspensions	2500 ± 246
Sugar-containing[a] drugs	5574 ± 594

[a]Sucrose, mannitol, glucose, and others.
(From Ref. [66].)

previous article and Golightly et al. have reviewed adverse effects associated with many inactive ingredients.[44,60]

Liquid medications, taken orally, can cause diarrhea and other GI symptoms, or they may aggravate GI distress that a patient is already experiencing. These GI effects can be associated with the high osmolality of some oral liquids. Osmolalities have been determined for various oral liquids.[66] For preparations containing propylene glycol, or various sugars (e.g., sucrose, mannitol, glucose), osmolalities were noted to be high (see Table 3). It is important to compare various brands of liquid medications because they may contain different excipients and may have different osmolalities.

Sustained-Release Preparations

Most medications have shorter half-lives in children than in adults, and therefore children may need sustained-release products to maintain serum concentrations in the therapeutic range. For example, a sustained-release theophylline product may be needed for a child with asthma. It may need to be administered every 8 h to the child as compared to every 12 h for a healthy, nonsmoking adult to maintain therapeutic serum concentrations. When choosing a sustained-release theophylline preparation for a child, it must be remembered that because of differences in release properties, theophylline sustained-release products are not interchangeable. A product selected for the pediatric asthma patient should be reliably absorbed with a minimal serum concentration variation and not a preparation that has exhibited a difference in bioavailability when administered with or without food.[67–69]

Extemporaneous liquid preparations

Because many medications are not available as liquid preparations, there are times when powder papers or suspensions must be prepared. An excellent information source about the preparation of liquid dosage forms for pediatric patients has been published by Nahata and Hipple (Nahata, M.C., Hipple, T.F. Pediatric Drug Formulations, 4th Ed. Harvey Whitney Books: Cincinnati, 2000).

Product selection

Products for oral administration should be in a dosage form most readily taken by the child. If the child is old enough to participate in the decision-making process, he or she may state a preference for a liquid, chewable tablet, tablet, or capsule, if the needed drug is available in a variety of dosage forms and appropriate dosage. If a liquid medication is needed, a product should be chosen based on texture, taste, and ease of administration. Other factors that must be considered are the absence of alcohol and dyes, and an osmolality that is close to physiologic (280–290 mOsm/kg). Are there excipients or adjuvants in the product, and if so, what are they and what is their concentration? Is there bioavailability information or pharmacokinetic information for the oral medication in pediatric patients, and if so, in what age groups? Is there information about the extemporaneous product that is to be prepared?

Rebecca Chater, a North Carolina pharmacist, recommends that pediatric patients be involved in medication counseling in order to improve their understanding of why a medication is needed. In the counseling process, the word medication should be used and not drug because of the connotation associated with the latter in today's society.[70,71] Chater recommends that, when possible, a product be selected that requires the fewest number of doses administered per day, for example, every 12 h dosing rather than every 8 h, so the medication does not need to be taken to school or day care for administration. If a medication must be given outside of the home, she recommends that two small labeled bottles be dispensed or one large bottle with a small empty bottle labeled to be used for medication administration at day care or school.

Health care providers including nurses, pharmacists, and physicians should demonstrate to parents and older children how medications should be administered and offer appropriate dosing devices (oral syringe, dropper, cylindrical medication spoon, or a small-volume doser with attachable nipple) to enable parents to accurately measure liquid products. A household teaspoon or tablespoon should not be used for medication administration because they are inaccurate. Kraus and Stohlmeyer[72] explain the use of a new oral liquid medication

delivery system that can be used for infants and young children who still use a bottle for feeding.

Administration Techniques

The following information is presented to help health care providers counsel parents and older children on how medication should be administered by various routes.

Oral liquids

An oral liquid medication needed for an infant or young child should be shaken well, if required, and then administered accurately using an appropriate device. If a dropper or an oral syringe is used, the liquid should be administered toward the inner cheek. Administration in the front of the mouth may allow the child to spit out the medication, whereas administration toward the back of the mouth may result in gagging or choking. The oral syringe should be of an appropriate size to allow for administration into the inner cheek.

Oral solid dosage forms

A medication available only as a solid dosage form, may be prepared as an extemporaneous liquid (e.g., suspension) or it may be modified for oral use, for example, by crushing. As mentioned previously, a sustained-release product should not be crushed or chewed. For a solid, nonsustained-release medication, the product can be crushed and mixed with a small amount of food just prior to administration. Examples of foods that may be used for mixing include applesauce, yogurt, or instant pudding, but the medication should not be added to an entire dish of food or to infant formula, because the infant

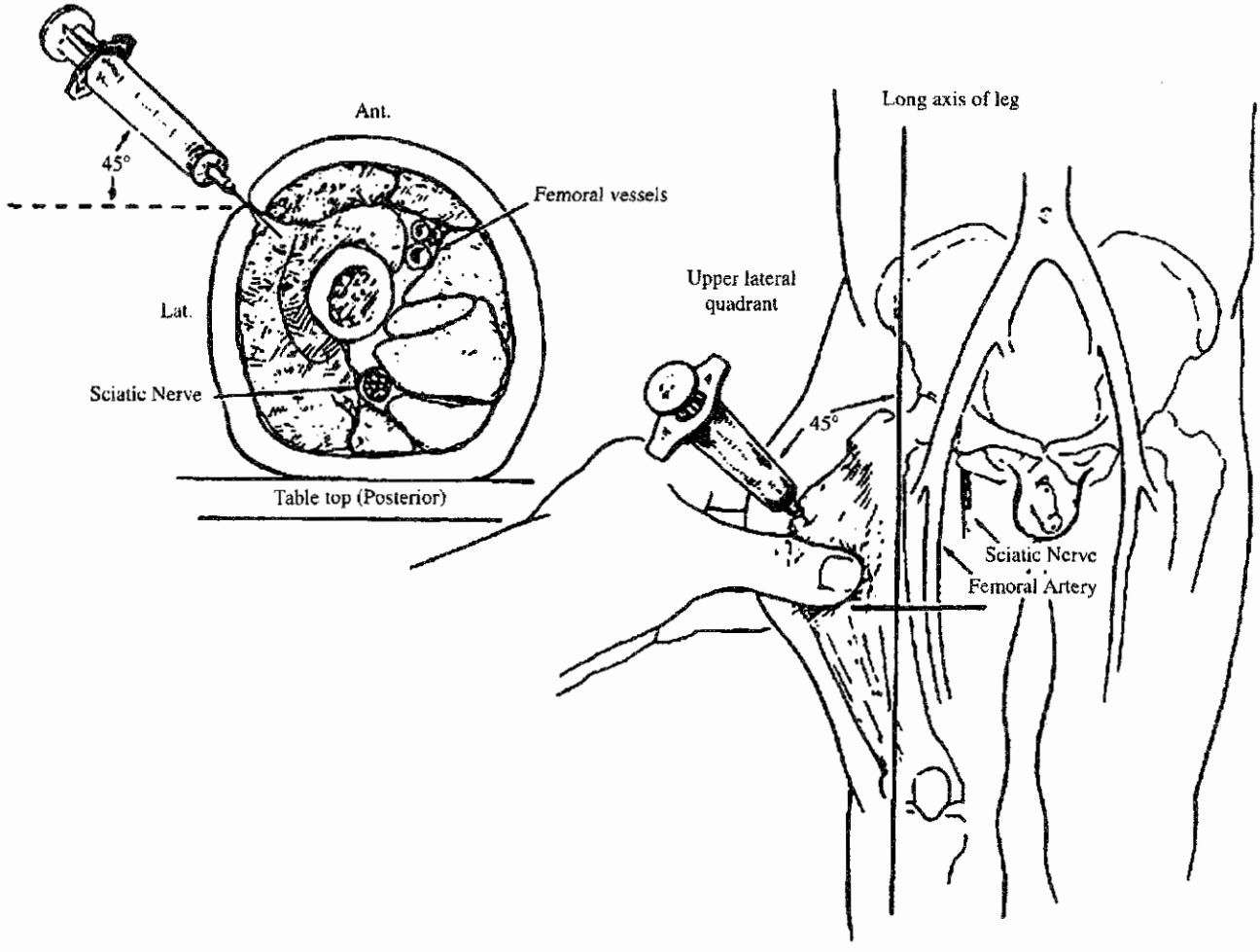

Fig. 5 A technique for anterior lateral-thigh intramuscular injection. (From Ref. [19].)

or child may not eat/drink the entire portion and thus not receive the total amount of medication.

OTHER ROUTES

Intramuscular Administration

Absorption of i.m. administered medications depends on the injection site because perfusion of individual muscle groups differs. For example, drug absorption from the deltoid muscle is faster than that from the vastus lateralis that is more rapid than from the gluteus.[16,17] In addition, lower perfusion or hemostatic decompensation, frequently observed in ill neonates and young infants, may reduce i.m. absorption. It may also be decreased in neonates who receive a skeletal muscle-paralyzing agent such as pancuronium because of decreased muscle contraction. In addition, the smaller muscle mass of neonates and young infants provide a small absorptive area.

The injection technique and the length of the needle used may affect drug absorption, and thus serum concentrations. For example, using a longer needle (1 1/2 vs. 1 1/4 in. or 3.8 vs. 3.1 cm.) for i.m. administration resulted in higher diazepam serum concentrations in adults.[18] Therefore, it is important to select the appropriate site for drug administration as well as the appropriate length and needle bore. Sites that can be used for i.m. administration include anterior thigh and vastus lateralis, gluteal area and deltoid.

The midanterior thigh (rectus femoris) and the middle third of the vastus lateralis are used for i.m. administration to young infants as well as to older children.[19] These sites are better developed and larger than other muscle groups that are used for drug administration to older children or adults. The technique is shown in Fig. 5.[19] With the patient lying supine, the "needle should be inserted in the upper lateral quadrant of the thigh, directed inferiorly at an angle of 45° with the long axis of the leg and posteriorly at a 45° angle"[19] to the surface on which the patient is lying. The person administering the injection should compress the tissues of the injection site to help stabilize the extremity. A 1-in. (2.5-cm) needle has been recommended for pediatric patients by Bergeson et al.[19] while Newton et al.[18] recommend a 23–26 gauge 11/2-in. (3.8-cm) needle. The volume of drug that can be administered in this manner is 0.1–1 ml in infants and 0.1–5 ml in older children and adults.[18]

The gluteal musculature develops as the infant or child increases his or her mobility; it becomes a more suitable injection site in children who are walking.[18,19] Damage to the sciatic nerve is the major problem associated with this injection site, and it occurs more commonly in infants because of their lack of gluteal muscle mass.[73] Injury to the gluteal nerve, resulting in muscle atrophy, has occurred even when the injection technique was appropriately performed.[19] Other nerves including the pudendal, posterior femoral cutaneous, and the inferior cluneal nerves have been damaged because of poor injection technique.[19] Additional adverse effects associated with this drug administration route are discussed by Bergeson et al.[19]

A technique for gluteal administration is shown in Fig. 6 although other techniques are also used.[19] All techniques involve the determination of the upper outer quadrant (see Fig. 6 for anatomical landmarks). After the location of the upper outer quadrant is determined, the needle should be inserted at a 90° angle to the surface on which the patient is lying.[19] This site can be used for older children. A 1-in. (2.5-cm) needle has been recommended.[19] The volume of drug that can be administered in this manner is 0.1–5 ml for older children and adults.[18]

The ventrogluteal (gluteus medius and minimus) site may be less hazardous for i.m. administration than the dorsogluteal (gluteus maximus) site.[19] The technique is shown in Fig. 7.[19] The person administering a drug i.m. ventrogluteally should first note the anatomical landmarks (anterior superior iliac spine, tubercle of the iliac crest, and upper border of the greater trochanter). The needle is

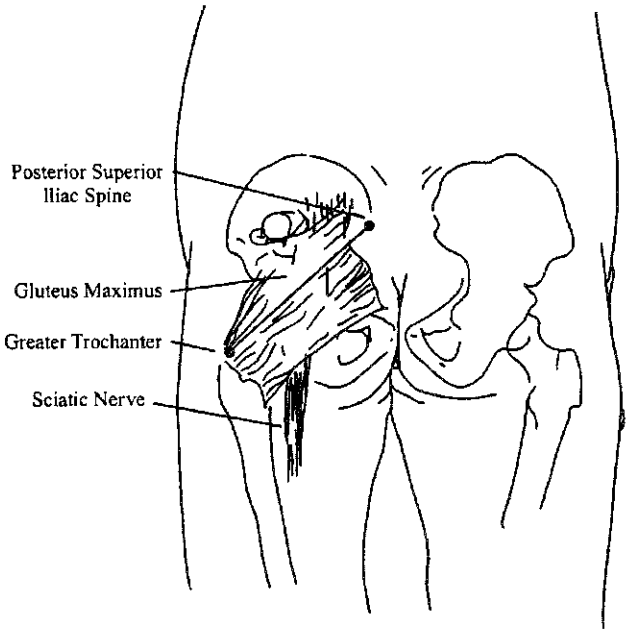

Fig. 6 A technique for gluteal-area intramuscular injection. (From Ref. [19].)

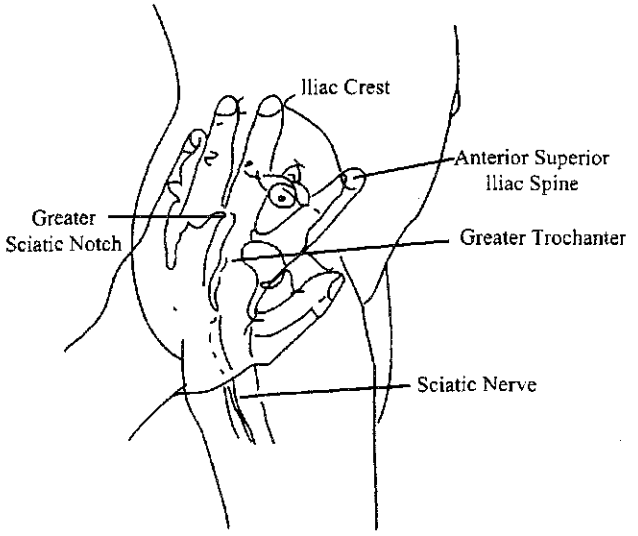

Fig. 7 von Hochstetter technique for ventrogluteal intramuscular injection. (From Ref. [19].)

inserted into a triangular area bounded by these landmarks while the patient is in the supine position. The location for this injection can be determined "by placing the palm over the greater trochanter, the index finger over the anterior superior iliac spine, and spreading the index and middle fingers as far as possible".[19]

The deltoid muscle can be used for i.m. injections in older children, but it is not an option for young infants and children because of their limited muscle mass. Although there are few complications associated with this administration route, nerve injury can occur.[21] The technique is shown in Fig. 8.[19] The area for deltoid administration should be fully visible so that the anatomical landmarks can be visualized. Then the needle for deltoid injection should enter the muscle halfway between the acromium process and the deltoid tuberosity to avoid hitting the underlying nerves.[19] The drug volume that can be administered by this route to older children and adults is 0.1–2 ml.[18] The recommended needle length for older children is 1 in. (2.5 cm).

Subcutaneous Administration

The s.c. route is used for drug administration, such as insulin, that requires slow absorption. It is not commonly employed for medication administration for pediatric patients but is used for specific drugs. Typically a 1/2- or 1-in. (1.25- or 2.5-cm) needle is used with the volume of drug that can be administered by this route ranging from 0.1 to 1 ml (drug volume administered depends on patient size).

Percutaneous Administration

The skin should be thoroughly cleaned prior to applying a topical ointment, cream, etc. A thin layer of ointment or cream should be applied to the prescribed area to reduce the possibility of a toxic reaction. The area of the skin where the medication is applied should not be covered or occluded unless instructed to do so by the physician because this procedure may increase drug absorption. Specific information should be given on how to cover the area.

Rectal Administration

Before the administration of a rectal suppository, the child's rectal area should be thoroughly cleaned. The infant or child should be placed on his or her side or stomach. The wrapper should be removed from the suppository and its pointed end should be inserted into the rectum above the anal sphincter. (If only half a suppository is prescribed, the suppository should be cut lengthwise before administration.) A finger cot or finger wrapped in plastic can be used for administering the suppository.[74] Because an infant or small child cannot adequately retain a suppository in the rectum, the buttocks can be held together firmly for a few minutes after rectal administration to hold the suppository in place.[74]

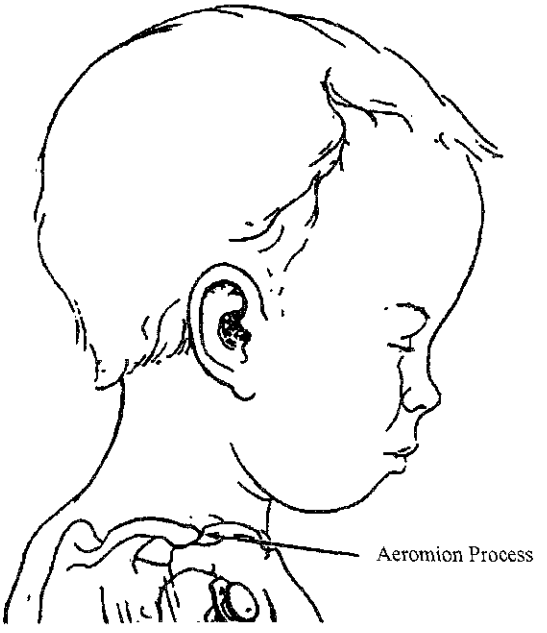

Fig. 8 A technique for deltoid intramuscular injection. (From Ref. [19].)

Otic Administration

Otic preparations should be at room temperature prior to administration. If the otic product is a suspension, it should be gently shaken for approximately 10 sec. before administration.[74] Prior to otic administration, the individual administering the medication should wash their hands thoroughly. The child should be lying on his or her side, and the earlobe should be gently pulled down and back to straighten the outer ear canal (for adults the earlobe is pulled up and back). Then the prescribed number of drops should be instilled into the ear without placing the dropper in the ear canal. The patient should be kept in a position with the ear tilted for approximately 2 min to help keep the drops in the ear.[75] This procedure may be repeated for the treatment of the other ear, if needed. The tip of the dropper should wiped with a clean tissue after use.

Nasal Administration

For adults, the first step in administering nose drops or a nasal spray is blowing the nose to clear the nasal passages of mucus and other secretions, but infants and young children are unable to do this. Therefore, the nasal passages may need be cleared with a bulb syringe prior to medication administration. A child should lie down on his or her back, or a young infant or child should be placed in a lying position, and the head should be tilted slightly backwards. An appropriate amount of medication should then be placed in each nostril. Thereafter, the infant or child should remain quiet for a few minutes to allow the medication to be absorbed. The dropper should be rinsed with hot water before it is returned to the medication container.

Ophthalmic Administration

An ophthalmic medication should be at room temperature prior to administration. If the eye drops are in a suspension, the container should be gently shaken before administration. A child old enough to follow directions should tilt his or her head slightly backward and to the side so that the eye drops will not drain into the tear ducts near the nose. The eyelids should be separated and the patient should be asked to look up. The appropriate amount of medication is instilled into the lower eyelid, using the medication dropper, which should be accomplished without touching the eyelids. The patient should look downward for a few seconds after drug administration. The eye(s) should then be closed for several minutes in order to spread the medication across the eyeball and be absorbed if the effect is to be systemic.[76] In addition, it has been recommended to gently put pressure on the inside corner of the eye for 3–5 minutes to retard drainage of the medication.[74] Do not use the eyedrops if they have changed color or if there is any particulate matter in the ophthalmic solution. The dropper should not be rinsed after use because this could lead to contamination of the dropper and the medication. The package insert should be reviewed for specific information.[76]

Another method for administering eyedrops to children recommends that the drops be applied to the inner canthus of the eye while the patient keeps his/her eyes closed until told to open them after medication administered.[77] Approximately 66% of the medication administered in this fashion was absorbed. In addition, this method may increase compliance and make children more cooperative.

For the administration of an ophthalmic ointment to a child who can cooperate, the child should tilt his or her head backwards and look up. After the hands have been washed, the person to administer the medication should squeeze out and discard the first 0.25 inches of ointment and discard it. Thereafter, the eyelid(s) should be gently pulled down for drug administration. A thin layer of ointment (0.25–0.5 inches) should then be placed in the lower eyelid(s). Afterwards, the eyelid(s) should be closed for 1 to 2 min to allow for the spreading of the medication and absorption. During this process, the tip of the ophthalmic applicator should not touch the eye. After administration is completed, the tip of the applicator tube should be cleaned with a clean tissue and be tightly capped.[76] The package insert should also be reviewed for specific information.

Inhalers

For the use of an inhaled medication (e.g., β2-agonists, corticosteroids, antivirals, cromolyn, etc.), it is crucial for the child and parents to understand the mechanism of the metered dose inhaler (MDI) or nebulizer, if used. The package insert should also be reviewed for information about the specific drug product. A decision may also need to be made as to whether a spacer may be needed for use with the medication canister.

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PROFESSIONAL DEVELOPMENT

Pediatric Pharmacy Specialty Practice

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INTRODUCTION

Providing pharmacy services to children can be challenging but also rewarding. The changes in body size and function that occur with normal growth and development result in a dynamic transition in drug disposition and therapeutic response throughout childhood and adolescence. In the past, there was little attention paid to these physiologic differences. Little information was available about the use of drugs in children; as a result, dosing and monitoring information were often extrapolated from studies conducted in adults. In fact, although nearly all drugs on the market in the United States were being used in pediatric patients, less than one-half carried a pediatric indication from the Food and Drug Administration (FDA).[1,2]

Since the 1980s, the lack of attention to pediatric-specific medication information has slowly changed as more data on dosing, pharmacokinetics, monitoring, and adverse effects in children have begun to appear in the medical literature. However, much research remains to be done. Many of the reports currently being published involve only small numbers of patients and often lack controls. Health care providers, including pharmacists, must be adept at drawing appropriate therapeutic information from these limited resources. In addition to the relative lack of medication information, pharmacists are frequently also faced with a lack of an appropriate dosage formulation. Most drug preparations on the market in the United States are designed for adults. These dosage forms must be tailored for use in children, often by compounding tablets or capsules into oral solutions, syrups, or suspensions.[3] Pediatric practice has evolved as a specialty within pharmacy to meet unique needs such as these in infants and children.

PRACTICE MODELS

There are many different types of pediatric clinical pharmacy positions. Although most pediatric clinical pharmacists work in a traditional hospital setting, many are branching out into ambulatory pediatric practice sites.[4,5] Clinic and retail pharmacy-based pediatric practitioners are finding a variety of ways to provide patient care. For example, many pharmacies now offer age-appropriate written and verbal patient/parent counseling and suggestions for improving medication compliance.[6] In either the acute or ambulatory setting, pediatric clinical pharmacists may be generalists, seeing children of many different ages with a variety of disease states, or specialize in a particular age or condition, such as neonates or children with pulmonary illnesses. Pediatric clinical pharmacists may also move into administrative and managerial roles. Other opportunities exist in the pharmaceutical industry, where pediatric clinical pharmacists may assist in the development or marketing of drugs for children.

The role of the pediatric pharmacist in organized health care has become well established. As early as 1971, reports of pediatric specialization in pharmacy were available.[7] Since that time, many more papers have been published describing pediatric practice models in both the hospital and retail settings.[4,6,8–10] In 1994, the American Society of Hospital (now Health-System) Pharmacists published guidelines for providing pediatric pharmaceutical services. Among the activities that the society recommended were the preparation of individualized doses, through the use of unit dosing and intravenous admixture systems, the provision of drug information and family education, and the maintenance of therapeutic drug monitoring and pharmacokinetic services. In addition, the group suggested that programs to provide ongoing evaluation of medication use and to orient and train pharmacy staff be established at each institution. The guidelines also call for the participation of pharmacists in clinical research involving children, both as investigators and as members of institutional review boards to ensure patient safety in drug trials.[5]

Whether hospital-, clinic-, retail-, or industry-based, it is becoming increasingly likely that the pediatric pharmacist will be involved in drug research. The need for pediatric-specific drug information and pediatric dosage

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006235

formulations has been targeted by the FDA.[11] In October 1992, the FDA took the first steps toward improving the amount of pediatric information available on drug labeling as part of their ruling entitled, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs: Revision of 'Pediatric use' Subsection in the Labeling." These new regulations were designed to promote the inclusion of information gained from new clinical trials as well as information gained from previously published studies and case reports in children. In an effort to support this research, a network of pediatric pharmacology units (PPRUs) were created at medical centers throughout the United States. Many of the PPRUs include pharmacists as investigators. Further progress was made in December 1994, when the FDA announced plans to mandate labeling information on pediatric use for all pertinent new drug applications. Manufacturers also were required to examine their existing products to determine if there was adequate cause to modify their pediatric sections to include more specific pediatric dosing and safety information.

As anticipated, this ruling generated considerable concern on the part of manufacturers who saw this as a potential roadblock to drug approval for adults patients and an additional expense. The FDA took a stronger stance on November 21, 1997, with the enactment of the Modernization Act. This ruling was the first major amendment of the Food, Drug, and Cosmetic Act and was designed to incorporate changes for the twenty-first century, including advances in technology and trade practices, as well as changing public health concerns. The Modernization Act covers many different aspects of the drug approval process, such as fast track policies, industry guidance, and postmarketing studies, but one of the most significant changes has been the tightening and enforcement of regulations relating to pediatrics. The complete Modernization Act became effective on April 1, 1999, and an increase in industry-sponsored research has already been observed. It is anticipated that the implementation of the Modernization Act will usher in a new era in pediatric drug research and provide opportunities for many pediatric pharmacists to contribute to the expansion of our knowledge of pediatric therapeutics.

DOCUMENTING BENEFIT

The benefits of having a clinical pharmacist within a pediatric practice setting have been documented in several different ways. Reducing medication errors and patient costs have been the primary methods by which new or additional pediatric pharmacy positions have been justified.[12,13] In 1987, Folli and colleagues published their study of the impact of pharmacy intervention on medication errors in two children's hospitals.[13] The pharmacists in this study detected, and prevented, mistakes at a rate of 5 errors per 1000 medication orders. The majority of the errors (64%) occurred in children younger than 2 years of age. This study received considerable attention in both the medical and lay press. It continues to serve as a landmark citation for the support of pharmacist participation in pediatric acute care. In addition to error prevention and cost savings, pediatric pharmacists have also documented their value in their contributions to our knowledge of medication use in children. It is now common for studies of new drugs in children to have at least one pharmacist author.[14–17] Pharmacists have also added to our knowledge of pediatric medicine by publishing case reports describing drug interactions and toxicities.[18] In addition, pharmacists have conducted studies of extemporaneous oral liquid formulations and intravenous drug compatibility, which have alleviated many of the problems with pediatric drug administration.[19,20]

PEDIATRIC PHARMACY RESOURCES

Pediatrics, unlike most other areas of pharmacy practice, encompasses a wide variety of disease states. Clinical pharmacists must not only have an understanding of the effects of growth and development on drug disposition, but also a general appreciation for therapies related to disease in any organ system. Despite the complexity of this patient age group, relatively little emphasis is given to pediatrics in most pharmacy school curricula. In a survey of pharmacy schools, an average of 16.7 hours was devoted to pediatric didactic content.[21] Most pediatric pharmacists develop their knowledge base in the clinical setting, beginning with experiential training during postgraduate programs and continuing throughout their careers. There are a number of resources available to provide information on pediatric medications for those beginning their study of pediatric pharmacy. Table 1 provides a list of topics that may serve as a guide for developing a basic knowledge of pediatric therapeutics.

Reference Texts

Fortunately for students and new practitioners, the pharmacotherapy texts most frequently required for didactic therapeutics courses contain introductory chapters on pediatrics.[22–24] These general chapters can be very helpful as brief overviews to pediatric specialty practice. General pediatric texts, such as the *Nelson Textbook of Pediatrics*, are also useful to provide a basic understand-

Table 1 Pediatric topics for clinical pharmacists

Growth and development
Drug dosage calculations and dosage formulations
Pediatric pharmacokinetics
Fluid and electrolyte management
Nutrition
Immunizations
Asthma
Cystic fibrosis
Infectious diseases
Management of fever
Otitis media
Sepsis and meningitis
Pneumonia
Diarrhea/dehydration
Urinary tract infections
Pediatric seizure disorders
Pediatric cardiology
Pediatric oncology
Pediatric endocrinology
Neonatology
Behavioral disorders
Pain management in infants and children
Cardiopulmonary resuscitation in infants and children

ing of pathophysiology in infants and children.[25] Although it has not been updated recently, the 1992 text *Pediatric Pharmacology: Therapeutic Principles in Practice* remains one of the best general references for pediatric drug information.[26] Another valuable reference is the Pediatric Module contained in the third edition of the *Pharmacotherapy Self-Assessment Program* (PSAP).[27] The PSAP program is designed to provide the reader with information on current and innovative clinical pharmacy practices. In addition to a basic chapter on pediatric pharmacotherapy, the module contains chapters on neonatology, critical care issues, respiratory infections, gastroenterology, and epilepsy. Additional pediatric topics are included in the first two editions. Each PSAP chapter also contains an annotated bibliography and self-test questions. More information on the PSAP program can be obtained through its publisher, the American College of Clinical Pharmacy, on their web site at www.accp.com.

Dosing Handbooks

All pediatric clinical pharmacists need access to current dosing handbooks. There are many dosing references available, but the most useful for pharmacists are those that also include information on administration, pharmacokinetics, and adverse effects, in addition to dosage and dosing frequency. Two examples of these references are the *Pediatric Dosage Handbook* and the *Handbook of Pediatric Drug Therapy*.[28,29] Both of these references contain thorough drug monographs as well as appendices with additional information on drugs for resuscitation, immunization schedules, and unit conversions. With the rapidly expanding information available on pediatric medication use, it is important to select dosing references that are frequently updated. A good rule of thumb is to choose those pediatric dosing handbooks that are revised at least every 2 to 3 years to incorporate new drugs and dosing information.

In addition to general dosing handbooks, the reference shelf for a pediatric clinical pharmacist may include several other more specific texts. Many clinicians use the report of the American Academy of Pediatrics Committee on Infectious Diseases as their standard reference for antibiotic and immunoglobulin therapy, as well as immunizations.[30] This report, often referred to as the "Red Book," is published approximately every 3 to 4 years. The *Pediatric Pain Management and Sedation Handbook* is also useful for pediatric pharmacists. This reference is filled with tables, nomograms, and algorithms to help clinicians to determine the appropriate drug, dose, and monitoring techniques for sedation and analgesia in a variety of settings.[31] For the preparation of intravenous medications, *Teddy Bear Book. Pediatric Injectable Drugs* is considered a standard reference.[32] This book contains single-page monographs with information on dosing, medication preparation, and infusion rates. Like the "Red Book," it is extensively referenced with citations from the original medical literature.

Pharmacists involved in patient/family teaching may also want to have written medication instructions available. The *Pediatric Medication Education Text* contains single-page instructions in English and in Spanish that can be photocopied for families of young patients.[33] These instructions meet the current FDA recommendations for written information and are designed to serve as a supplement to verbal medication counseling. The information in this book is targeted at patients younger than 12 years of age. For example, instead of containing warnings against driving for those drugs causing dizziness or sedation, these sheets instruct parents to watch children closely when they are going up or down stairs. Another frequently used reference for family counseling is *Drugs in Pregnancy and Lactation*.[34] This text, also available on CD-ROM, contains brief summaries of the literature regarding the potential for teratogenicity during pregnancy and toxicity during breastfeeding. In addition to presenting the results of case reports and small-scale studies, this reference also includes the outcomes of surveillance studies conducted in the United States and fo-

reign countries, such as Canada's MotherRisk program. Like many of the handbooks and references described earlier, this text lists drugs by generic name in alphabetical order, making it easy to use for quick consultations. A separate quarterly update subscription is also available from the publisher.

Journals

There are many pediatric medical, nursing, and pharmacy journals that include articles on pediatric drug therapies (Table 2). *Pediatrics*, the journal of the American Academy of Pediatrics (AAP), and the *Journal of Pediatrics* are considered by most pediatric practitioners to be the top in the field. *Pediatrics* is of particular use to clinicians because it includes the policy statements developed by the AAP. These statements are considered to represent standards of practice by pediatricians. Many of these statements are also of interest to clinical pharmacists, such as the yearly schedule for routine childhood immunizations.[35] Other AAP policy statements of note include recommendations on the administration of medications during breastfeeding,[36] the ethical treatment of children enrolled in clinical research trials,[37] and methods to reduce medication errors in the pediatric inpatient setting.[38] The *Journal of Pediatrics* has also published useful practice recommendations, such as the guidelines for antithrombotic therapy.[39] The pediatric journal for the American Medical Association, *Archives of Pediatrics and Adolescent Medicine*, often contains large-scale surveillance studies such as a retrospective review of methylphenidate toxicity.[40] These policy statements, guidelines, and reviews will make useful additions to the files of most pediatric clinical pharmacists.

Table 2 Examples of peer-reviewed journals containing articles on pediatric therapeutics

American Journal of Health-System Pharmacy
Annals of Pharmacotherapy
Archives of Diseases in Childhood
Archives of Pediatrics and Adolescent Medicine
Clinical Pediatrics
Clinical Pharmacokinetics
Current Pediatric Therapy
Drug Safety
Drugs
Journal of Pediatrics
Journal of Pediatric Pharmacology and Therapeutics (formerly *The Journal of Pediatric Pharmacy Practice*)
Paediatric Drugs
Pediatric Clinics of North America
Pediatric Emergency Care
Pediatric Infectious Disease Journal
Pediatric Nursing
Pediatrics
Pharmacotherapy

Web Sites

A growing number of web sites have been developed for pediatric medication information. Most university teaching hospitals and children's medical centers have web sites that include educational programs. For example, the University of Virginia Children's Medical Center web site offers tutorials for health care providers on attention deficit/hyperactivity disorder and cerebral palsy, as well as the institution's *Pediatric Pharmacotherapy* newsletter.[41] In addition, many professional organizations for pediatric health care practitioners have web sites, as well as mailing lists, chat rooms, or electronic bulletin boards. Two other useful resources on the Internet are PEDINFO and Harriet Lane Links, the latter sponsored by The Johns Hopkins University. These two noncommercial web sites provide a large number of links to pediatrics-related sites, as well as some feedback on the quality of information contained on many of the linked sites. Table 3 lists these web sites and several others that may be of interest to pediatric clinical pharmacists.

PROFESSIONAL ORGANIZATIONS FOR PEDIATRIC PHARMACY PRACTITIONERS

There are several organizations that provide educational programs and networking opportunities for pediatric clinical pharmacists. Two of the most active groups are the Pediatrics Practice and Research Network (PRN) within the American College of Clinical Pharmacy (ACCP) and the Pediatric Pharmacy Advocacy Group (PPAG). The ACCP Pediatrics PRN currently has approximately 200 members and meets twice yearly at the ACCP Spring Forum and annual meetings. The focus of the Pediatrics PRN is to support the practice, teaching, and research of its members by fostering collaboration and sharing information among colleagues. For more information about this group, visit the ACCP web site at www.accp.com.

PPAG was also founded by pharmacists practicing in pediatrics. Although this group has traditionally been focused on issues related to hospital practice, with an emphasis on pharmacy administration, the past several years have seen a renewed interest in expanding the organization and incorporating clinicians from a variety of practice settings. PPAG holds an annual meeting and also sponsors a meeting in conjunction with the American Society of

Table 3 Websites of interest to pediatric clinical pharmacists[a]

Source	URL
Agency for Healthcare Research and Quality	www.ahrq.gov
American Academy of Pediatrics	www.aap.org
American College of Clinical Pharmacy	www.accp.com
Centers for Disease Control and Prevention	www.cdc.gov
Food and Drug Administration (FDA)	www.fda.gov
FDA Pediatric Medicine Page	www.fda.gov/cder/pediatric/index.htm
Harriet Lane Links	www.med.jhu.edu/peds/hll
Institute for Safe Medication Practices	www.ismp.org
Kids Meds	www.kidsmeds.org
MedWatch (Adverse Event Reporting)	www.fda.gov/medwatch
Neonatal and Paediatric Pharmacists Group	www.nppg.demon.co.uk
Pediatric Critical Care Medicine	www.pedsccm.org
Pediatric Pharmacy Advocacy Group	www.ppag.org
PEDINFO	www.pedinfo.org
U.S. Pharmacopeia: Children and Medicine	www.usp.org/information/programs/children
Vaccine Adverse Event Reporting System	www.vaers.org

[a]Accessed June 2002.

Health-System Pharmacists' Clinical Midyear Meeting. PPAG also organizes the Pediatric Adverse Drug Reaction Program (PADR), a central database of adverse effects in children. For more information about this group, visit their web site at www.ppag.org. Both the ACCP Pediatrics PRN and PPAG offer a wide array of member services, including mailing lists for communication among their members. An international group, the Neonatal and Paediatric Pharmacists Group (NPPG), may also be of interest. This organization was formed in 1994 to advance the quality of pharmacy services for children in the United Kingdom. Their web site (www.nppg.demon.co.uk), offers links to a variety of resources and bulletin boards for subgroups in oncology, as well as pediatric and neonatal intensive care.

CONCLUSION

Pediatric pharmacy practice has come a long way since Shirkey first coined the term "therapeutic orphans" to describe the lack of information and research support for children requiring medications.[42] As we begin the twenty-first century, there are a growing number of pediatrics drug resources available to the health care provider. We have seen the benefits of increased information in the medical literature, the publication of several pediatric-specific dosage handbooks, and the advent of the Internet as a means of sharing information with colleagues. These changes, along with a renewed interest from the FDA in pediatric drug research, are coming together to allow pediatric practitioners to expand our knowledge of drug disposition in children and improve the quality of their health care.

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Pew Health Professions Commission Reports

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INTRODUCTION

The Pew Commission Reports are a series of forward-looking documents that critically examine the education and training of health professionals in the context of the most dynamic decade ever faced by the nation's healthcare providers. Anchored by four "Commission" reports, the series is complemented by public policy papers, task force recommendations, and research reports on such topics as accreditation of educational programs,[1] regulation of the healthcare workforce,[2] and federal graduate medical education.[3]

ABOUT THE COMMISSION

Established in 1989 by the Pew Charitable Trusts[4] and administered initially at Duke University and later at the University of California–San Francisco's Center for the Health Professions, the Commission was "inspired by the belief that the education and training of health professionals is out of step with the evolving health needs of the American people." Since its inception, five values have guided the Commission's work:

- Universal access to basic healthcare services coordinated by the states, but implemented and supported by combined federal, state, and private resources.
- More efficient use of resources to better manage capacity and the outcomes of care while using best practices and reducing duplication.
- Socially desired outcomes based on empirical evidence.
- Creativity and innovation through experimentation with new providers, technologies, administrative structures, and ways to involve the patient within a modern regulatory framework.
- Informed choice and greater public responsibility through better use of information, decision making, and incentives for behavioral change.

The Commission Reports

The first Commission Report, *Healthy America: Practitioners for 2005*,[5] set the stage for the Commission's ten-year agenda by establishing the premise that reform of the system that prepares health professionals is central to crafting good healthcare policy for the nation. It described a framework for change within its view of evolving healthcare trends, laid out specific challenges to health profession educators and administrators, and proposed an agenda for action. The Commission made it quite clear that the success of its work was dependent on broad-based input and participation from all stakeholders, and it established advisory panels and health and public policy task forces, and launched research activities supporting its work.

The following three reports built on this initial framework. Each provided an updated snapshot of the evolving healthcare system in the United States including sections on access, quality, financing, and satisfaction. These sections were generally followed by observations and general recommendations to the healthcare and health profession education systems, followed by specific recommendations to individual professions.

Perhaps the most thoughtful and valuable contribution of the Commission was its 1993 presentation *Health Professions Education for the Future: Schools in Service to the Nation*[6] and subsequent revisions of competencies (Table 1) for successful practice in the 21st century. This effort has been used uniformly across the health professions by schools, professional associations, accrediting agencies, and regulatory bodies.

Critical Challenges: Revitalizing the Health Professions for the Twenty-first Century,[7] the Commission's third report published in 1995, noted that while the federal government was unable or unwilling to reform the healthcare system, a number of market-driven forces were at work directly challenging the high costs of the system. The most controversial recommendations in this Report centered on the belief that an oversupply of health professionals was imminent: The numbers of health pro-

Table 1 Twenty-one competencies for the twenty-first century

Embrace a personal ethic of social responsibility and service.
Exhibit ethical behavior in all professional activities.
Provide evidence-based, clinically competent care.
Incorporate the multiple determinants of health in clinical care.
Apply knowledge of the new sciences.
Demonstrate critical thinking, reflection, and problem-solving skills.
Understand the role of primary care.
Rigorously practice preventive healthcare.
Integrate population-based care and services into practice.
Improve access to healthcare for those with unmet health needs.
Practice relationship-centered care with individuals and families.
Provide culturally sensitive care to a diverse society.
Partner with communities in healthcare decisions.
Use communication and information technology effectively and appropriately.
Work in interdisciplinary teams.
Ensure care that balances individual, professional, system, and societal needs.
Practice leadership.
Take responsibility for quality of care and health outcomes at all levels.
Contribute to continuous improvement of the healthcare system.
Advocate for public policy that promotes and protects the health of the public.
Continue to learn and to help others to learn.

fessionals entering practice should be reduced by closing schools in medicine, nursing, and pharmacy.

The Commission's final recommendations were presented in its fourth report. *Recreating Health Professional Practice for a New Century*[8] built on previous work and, as with earlier reports, suggested a strategic guide for changing schools, regulations, and professional practice.

THE COMMISSION AND PHARMACY

From the outset, pharmacy practice and pharmaceutical education figured in the Commission's agenda. In 1990, preceding its first report, *Perspectives on the Health Professions*[9] was commissioned and the chapter on pharmacy authored by Jack R. Cole and Jere E. Goyan. It described pharmacy's evolution as a profession, and presented the contemporary challenges facing pharmacy education and practice. Like other chapters, it served to identify common themes and initiate a dialog between the Trusts, professional leadership, and Commission staff.

Dr. Goyan also participated in the deliberations resulting in the first and second Commission Reports. In the first Report, little about pharmacy was specifically published except for the results of survey research quantifying pharmacists' perceptions of their education. Rather, a continuing case was being built for the inclusion of medication use within the context of responsible healthcare. Clearly the trends affecting healthcare in general (i.e., coordinated care, diversity and aging, expansion of science and technology, consumer empowerment) would have a profound impact on pharmacy. The second Report dedicated a chapter to pharmacy and introduced the term "pharmaceutical care" as a "responsible and participatory" process to a broader audience outside of the profession. It was no easy task to suggest that pharmacists "contribute to the drug therapy decision-making process, including the determination of dose, schedule, form, and delivery method; provide the medication; and monitor patient compliance, progress, and outcomes."

Specific strategies recommended in the second Report included curricular reform, documentation of pharmacist–patient–physician interactions, medication-use information systems, clinical training in non-institutional sites, and faculty development. These strategies provided guidance and supported the work of the American Association of Colleges of Pharmacy's Commission to Implement Change in Pharmaceutical Education[10] and its Center for Advancement of Pharmaceutical Education.

As previously described, the third Report offered a radical recommendation for pharmacy: "Reduce the number of pharmacy schools by 20–25% by the year 2005." The rationale for this recommendation, supported with preliminary data, was several-fold:

- Managed care would require a knowledge base and skill set different from contemporary pharmacy practice, more aligned with clinical pharmacy and pharmaceutical care.
- Technology, robotics, and technicians could do the manipulation-intensive work of pharmacists more efficaciously.
- Schools were perceived to be moving too slowly to get in step with the evolving healthcare needs of the American people. A less controversial recommendation suggested that pharmaceutical education focus even more on issues of clinical pharmacy, system management, and working with other healthcare providers.

As one of its five case studies, the third Report highlighted pharmaceutical care in education and practice. The Commission specifically chose to offer pharmaceutical education's experience in the decade:

> The process of educational evaluation and reform that has accompanied this professional evolution can serve as an

example as other health professions re-examine their missions in light of ongoing changes in the health care delivery system.

The fourth Report set forth three recommendations for pharmacy, each supporting the views of previous Commission's work:

- Continue to orient pharmaceutical education to reflect pharmacists' changing practice roles and settings under managed care and in clinical drug therapy. Referenced within this recommendation are various elements of the 21 competencies and more emphasis on residency training.
- Embrace an interdisciplinary approach to healthcare. Again the competencies are referenced as well as collaboration with pharmacy technicians and other allied health workers.
- Provide opportunities for re-training and continuing education for practitioners to develop skill sets for expanded clinical roles beyond dispensing pharmaceuticals. Included in this recommendation is greater emphasis on distance education and collaboration with managed care and chain pharmacy settings in developing and delivering re-training programs.

The Pew Charitable Trusts also supported other pharmacy-based initiatives during the 1990s, which were stimulated by the work of the Commission. The Pharmacy Manpower Project[11] worked with state boards of pharmacy to establish a method for monitoring supply and determining base-line numbers of and demographics for practicing pharmacists. The Scope of Pharmacy Practice Project[12] provided a contemporary update to an earlier study that described what pharmacists do in various practice settings. The results of these efforts, and their respective databases, are available to researchers for continuing analysis.

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Pharmaceutical Benefits Scheme (Australia)

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INTRODUCTION

The Pharmaceutical Benefits Scheme (PBS) is the Australian Federal Government program that provides public subsidy of a range of medications determined to meet safety, quality, effectiveness, and cost-effectiveness criteria. The PBS is available to every Australian resident and visitors from countries that have reciprocal healthcare agreements with Australia. PBS medicines can be prescribed for patients in ambulatory and aged care settings and in private hospitals. An alternative funding program is utilized in government funded hospitals. The Repatriation Pharmaceutical Benefits Scheme (RPBS) is an enhanced version of the PBS available to eligible war veterans and war widows.[1]

Under the program the government: 1) negotiates a price for a medicine with the supplier of the product; 2) controls the mark-ups applied at all stages of the supply chain; and 3) subsidizes the cost of the medicine to patients where the price exceeds certain limits. The subsidies are linked to the welfare needs of the patient and a safety net provides protection for high users of medication.

A number of programs have been introduced to the PBS that are aimed at improving the prescribing and utilization of medication. An example relevant to pharmacy is the Medication Management Program under which accredited pharmacists are remunerated for conducting medication reviews in both aged care and domiciliary settings. Under the Pharmacy Development Program, funding grants are provided to pharmacies achieving quality accreditation, for research into professional pharmacy services and, in the near future, for expanding the provision of medication information to consumers.

APPROVAL OF MEDICINES

Two separate branches of the Department of Health and Family Services determine which medicines are approved for use in Australia and which will be subsidized via the PBS. The Therapeutic Goods Administration is responsible for assessing medicines for quality, safety, and efficacy in order to approve them for marketing. Once approved for marketing, the sponsor (manufacturer) of the medication may apply to the Pharmaceutical Benefits Advisory Committee (PBAC) of the Pharmaceutical Benefits Branch to list the medicine on the Schedule of the PBS. The PBAC is an independent statutory body that applies cost-effectiveness criteria in determining if a medicine will be included on the PBS and any restrictions that are to apply to its use.[2]

On its inception in 1948 the PBS funded 139 "life-saving and disease preventing drugs." By May 2000 the Schedule included 581 generic drugs available as 1,417 dosage forms and strengths marketed as 2,102 branded products.[3] It is estimated that 75% of prescriptions in the ambulatory care setting are for medicines listed on the PBS. The PBS has wide spread public support and bipartisan political support.

PBS PRESCRIBING AND DISPENSING

PBS listed medicines are eligible for subsidy if they are prescribed by a registered medical practitioner or, for certain medicines, a registered dental practitioner, in accordance with the regulations governing the scheme. The prescription must be dispensed by an approved pharmacist or, in limited cases, by an approved medical practitioner. The vast majority of medical practitioners, dentists, and pharmacists involved with the scheme are private practitioners.[4]

The PBS includes a set of general prescribing and dispensing regulations aimed at standardizing practices, simplifying processes, and minimizing waste and abuse. For example, a prescriber can not write more than one prescription for the same medicine for the same patient on the same day. Similarly, there are specified periods that must elapse before a pharmacist can dispense a second prescription of the same medicine for the same patient.[4]

In addition to the general regulations, there are specific regulations that apply to particular medicines. The maximum quantity of a medicine and maximum number of times a medicine can be dispensed per prescription are

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DOI: 10.1081/E-ECP 120006365

specified depending on the type of medicine. In general terms, medicines for chronic diseases can be prescribed in quantities adequate for one month of treatment at standard doses with five repeat supplies providing a total of six months of therapy per prescription. The maximum PBS quantities for medicines for acute conditions reflect standard treatment periods. Manufacturers supply most medicines in packs corresponding to the PBS maximum quantities.[4]

Medicines listed in the PBS Schedule fall into three categories of restriction: 1) Unrestricted medicines can be prescribed at the discretion of the medical practitioner; 2) restricted medicines should only be prescribed for specific therapeutic uses; and 3) authority medicines are also restricted to specific therapeutic uses but can only be prescribed following approval from a government agency.[4]

PRICES AND SUBSIDIES

The federal government has used its position of dominant funder in the prescription market to negotiate prices for medication that historically have been 30–40% lower than in the United States and Western Europe. Wholesale distributors and pharmacists are allowed to add specified mark-ups, and pharmacists also receive a professional dispensing fee resulting in the "PBS dispensed price." In 1999, the average PBS dispensed price was $26.35, which equated to 3.65% of average weekly earnings.[5,6]

Most patients pay a co-payment toward the PBS dispensed price. Neither the price nor the therapeutic use of the medicine is a factor in determining the level of the co-payment. There is one level of co-payment for general patients and a lesser one for patients with concessional status. General patients pay the cost of the dispensed medicine up to a maximum of $21.00. All people of retirement age, on pension, receiving unemployment or welfare benefits, and all Veterans pay the concessional co-payment of $3.50 per medication (year 2001 rates). After dispensing a prescription, the pharmacist submits it to the Federal Government's Health Insurance Commission, which pays to the pharmacist the PBS dispensed price less the applicable patient co-payment. If a family unit requires chronic medication and reach expenditure thresholds on PBS prescriptions approximating either 30 or 50 prescriptions per calendar year, a stepped safety net scheme provides a higher level of subsidy. At maximum safety net benefit, the patient co-payment is eliminated.[7]

In 1999, the concessional patient contribution (then $3.20) represented 14% of the average PBS dispensed price of concessional prescriptions, and the general patient contribution ($20.30) represented 40% of the average PBS dispensed price of general prescriptions. Each Australian has on average six prescriptions for PBS medicines each year; however concessional patients have an average of 20 prescriptions per year, resulting in 79% of government expenditure on the PBS being directed to concessional patients.[6]

In the mid-1990s, expenditure on pharmaceuticals—largely expenditure on PBS listed medicines—accounted for 15% of total healthcare expenditure in Australia, which was 8.5% of gross domestic product. Of the total outlays on the PBS, manufacturers receive 67%, pharmacists 26%, and wholesalers 7%.[7]

Although the government's dominant position has enabled it to maintain relatively low costs for individual medicines, the PBS is an uncapped government program in which the level of overall government subsidy is largely driven by doctors' prescribing habits. With the introduction of new drugs that have benefits over older, cheaper medicines and with a population that is aging, the government outlay has increased rapidly. In the seven years from 1992 to 1998, the cost to the government of PBS prescriptions increased by 107%. An increase in prescription volumes of 6.5% in calendar 1999 over the previous year resulted in a further increase in government expenditure of 14.5%.

Brand Price Premiums and Brand Substitution

Different brands of the same drug may be listed in the PBS Schedule at different prices and the federal government subsidizes up to the price of the lowest priced brand. As a result of this policy, patients are required to pay a surcharge on their patient co-payment if they choose the higher priced brand of a drug when a lower priced generic exists.

This policy promotes generic substitution and pharmacists are allowed to substitute a bioequivalent medicine without reference to the prescriber if the patient agrees and the prescriber has not vetoed such substitution.[4]

Therapeutic Group Premiums

This policy extends the principle of brand price premiums to four therapeutic groups of medicines that are clinically similar. The groups are angiotensin converting enzyme inhibitors, calcium channel blockers, HMG CoA reductase inhibitors, and H2 receptor antagonists. There is at least one drug in each group available at the basic patient co-payment without supplementary charge.[4]

Both the Brand Price Premium and Therapeutic Group Premium policies are aimed at establishing benchmark prices within equivalent groups of medicines and promoting use of the cheapest of the options available.

REVIEW OF PBS LISTING OF MEDICINES

The PBS gives priority to listing of medicines for the treatment of conditions not amenable to self diagnosis and treatment. Consequently if a particular medicine or a group of medicines no longer requires prescriptions, it may be delisted from the PBS schedule. Similarly if medicines are deemed to be no longer an acceptable or cost-effective therapeutic choice, they may be delisted. Examples of delisting include all antihistamines, all preparations containing dextropropoxyphene, and all nasal sprays.

MEDICATION MANAGEMENT PROGRAM

The Medication Management Program (MMP) provides federal government funding for accredited pharmacists to undertake medication reviews. The aims of the reviews are to:

- Contribute to optimizing the therapeutic effectiveness and manageability of the medication regimen.
- Facilitate a cooperative working relationship between pharmacists and other members of the healthcare team in order to benefit the health and well being of the patient.
- Provide an information resource for colleagues in relation to patients' medications and the medication review process.[8]

A medication review involves the systematic evaluation of the patient's complete medication regimen including clarification of the indications for use and administration details of both prescription and non-prescription medicines plus the outcome of therapy. The process results in the generation of a report by the pharmacist documenting interventions and recommendations to other healthcare providers to optimize therapeutic outcomes.

The MMP replaced the Medication Review Program. Under the initial program pharmacists were funded to undertake systematic medication reviews for residents of aged care facilities (nursing homes and supported care hostels). The MMP increases the level of funding per review episode and introduces funding for medication reviews for domiciliary patients. While reviews in the aged care facility setting are at the initiation of pharmacists, reviews in the domiciliary setting are on referral from a medical practitioner.

Under this program pharmacists are being remunerated for their clinical expertise rather than for the supply of medicines. The federal government has determined that the cost of this program will largely be met out of savings in expenditure on PBS medicines as a result of rationalization of prescribing following the medication reviews.[9]

Other clinically focused services that are to be funded via the MMP include case discussions between pharmacists and medical practitioners and support for pharmacists to work within divisions of general practice as part of an integrated, geographically based primary healthcare service.

PHARMACY DEVELOPMENT PROGRAM

The Pharmacy Development Program (PDP) provides federal government support for programs of quality accreditation of pharmacies, for the provision of medicine information for consumers, and for research programs to identify cost effective professional pharmacy initiatives that can demonstrate net benefits for the Australian health system.

With this federal government support, professional pharmacy bodies have established practice standards, measurable performance indicators, and pharmacy accreditation programs. The standards address health promotion, drug dispensing, dose administration aids, patient counseling, compounding, medication reviews, comprehensive pharmaceutical care, drug information services, liaison pharmacy, and pharmacy services in residential care facilities.[10]

Funding arrangements for the accreditation and medicine information services are currently under negotiation but will take the form of block grants to accredited pharmacies.

The MMP and PDP are funded partly from the general revenue of the federal government and partly by the transfer of funds from projected growth in remuneration to pharmacists for dispensing of PBS prescriptions. As such, pharmacists are being remunerated for services aimed at improving the use of medication at the expense of growth in their remuneration from dispensing medication.

The total of the funds available for pharmacists' clinical practice via the MMP and PDP is small in comparison with the total PBS expenditure; however, both

government and professional organizations support continued expansion in these areas.[11]

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PROFESSIONAL DEVELOPMENT

Pharmaceutical Care

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INTRODUCTION

As defined by Hepler and Strand in 1990, "pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life."

A revised definition provided in 1998 states that "pharmaceutical care is a practice in which the practitioner takes responsibility for a patient's drug-related needs and is held accountable for this commitment. In the course of this practice, responsible drug therapy is provided for the purpose of achieving positive patient outcomes."

The desired outcomes of pharmaceutical care are as follows: 1) cure of a patient's disease; 2) reduction or elimination of disease symptoms; 3) arresting or slowing progression of a disease; and 4) preventing a disease or symptoms. These outcomes are achieved through the identification and resolution of drug therapy problems.

HISTORY OF LANDMARK DEVELOPMENTS

In their seminal paper on pharmaceutical care, Hepler and Strand described the evolution of the pharmacy profession from traditional apothecary functions in the early twentieth century to dispenser of medications in the 1950s, and through the clinical pharmacy movement beginning in the mid-1960s. The concept of pharmaceutical care represents the culmination of this professional maturation from a primary focus on the dispensing and administration of drug products to the acceptance of a social responsibility for the health care needs of individual patients.

This new practice is required to meet an unfilled need in the health care system that has developed in part because of rapid increases in the number and complexity of available drug products. These therapeutic advances can improve health and may prolong life, but their use is also associated with a commensurate increase in the risk of preventable drug-related morbidity and mortality. In a 1995 study of the U.S. health care system, the estimated yearly costs associated with managing drug-related morbidity and mortality exceeded $76 billion in outpatient settings. The same study estimated that approximately 28% of hospital admissions resulted from drug-related problems. In 1999, the National Institute of Medicine estimated that 7000 patients die each year from medication errors that occur both within and outside hospitals.

To reduce medical problems associated with drug use, a rational decision-making process for drug therapy must be established, and a health care practitioner is needed to systematically apply this approach. The pharmacy profession recognizes the need to improve drug therapy outcomes, and since 1990 it has gradually moved toward adopting pharmaceutical care as the mission of pharmacy practice. The American Pharmaceutical Association (APhA), American Society of Health-System Pharmacists (ASHP), American Association of Colleges of Pharmacy (AACP), and Federation Internationale Pharmaceutique (FIP) have embraced the principles of pharmaceutical care. In 1998, the Alliance for Pharmaceutical Care was founded and now consists of 10 pharmacy organizations. Its purpose is to demonstrate to state legislators that patient care services provided by pharmacists can improve medication use and reduce health care costs associated with drug-related problems.

Pharmaceutical care is very different from other cognitive patient care services such as clinical pharmacy and disease state management programs. It is not a separate service that is superimposed on an existing practice but a comprehensive professional practice much like medicine and nursing. Consequently, it has a clearly defined philosophy of practice, patient care process, and practice management system. The remainder of this article describes the essential principles and processes involved in the practice of pharmaceutical care.

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DOI: 10.1081/E-ECP 120006330

PRINCIPAL CONCEPTS

Pharmaceutical Care as a Generalist Practice

Pharmaceutical care is a *generalist* practice in which the practitioner takes responsibility for providing consistent, ongoing, comprehensive care to a population regardless of age, gender, medical problem, drug class, or organ system disease. Care is not provided to some patients but not others because of time constraints, convenience, or simply personal preference. The practitioner is responsible for ensuring the appropriateness of *all* aspects of a patient's drug therapy. Moreover, each patient receives care that meets the same standard of quality. The generalist practitioner seeks the expertise of a specialist only when complex drug therapy problems exist that exceed the generalist's knowledge, skills, or experience.

Application to All Practice Settings

The principles and processes of pharmaceutical care practice are needed and applicable to patients in all pharmacy settings, including (but not limited to) inpatient, outpatient, community pharmacy, and academic sites. Practice is not restricted to select pharmacists based on years of experience, degree, specialty practice certificate, board certification, residency experience, or academic appointment. It is not a function of professional credentials or place of work but rather the desire and competence to take responsibility for the outcomes of each patient's drug therapy.

Creation of Collaborative Partnerships

Pharmaceutical care is a necessary component of the existng health care system and must be integrated with other aspects of health care. The pharmacist cooperates with the patient and other health care professionals but does not have sole responsibility for the medication use process. Other health professionals (e.g., physicians, nurses) also have clearly defined roles related to proper medication use. The concept of pharmaceutical care does not imply a reduction or elimination of those roles. In fact, qualified health care providers other than pharmacists can provide pharmaceutical care. However, pharmacists possess knowledge and skills that make them uniquely suited to assume the responsibility for reducing drug-related morbidity and mortality.

Consistency with Other Health Care Practices

Pharmaceutical care is a professional *practice* that addresses a unique set of health care needs not currently addressed by other practitioners. A practice is the application of a specialized set of knowledge to resolve specific patient problems in accordance with standards accepted by both the profession and society. These standards require that the patient care process be completed in its entirety for each patient. Pharmaceutical care practice shares three attributes common to all health care practices: 1) a single philosophy of practice; 2) one patient care process; and 3) a practice management system.

Philosophy of Pharmaceutical Care Practice

The practice of pharmaceutical care has a clearly articulated philosophy that defines values and explains *what* all practitioners must do. According to this philosophy, the practitioner performs the following: 1) takes responsibility for meeting society's need to reduce drug-related morbidity and mortality; 2) employs a patient-centered approach that addresses *all* the patient's drug-related needs; 3) establishes a caring therapeutic relationship with individual patients; and 4) assumes a clearly defined set of responsibilities that directs patient care activities. These responsibilities are to ensure that patients receive the most appropriate, effective, safe, convenient, and economical therapy; to identify, resolve, and prevent drug therapy problems; and to ensure that optimal patient outcomes are achieved.

Patient Care Process

The patient care process (Fig. 1) describes *how* an individual practitioner fulfills the responsibilities delineated in the philosophy of practice. This process includes three distinct elements that must be completed for each patient: 1) patient assessment; 2) creation of a pharmaceutical care plan; and 3) follow-up evaluation. The success of the process depends on the quality of the therapeutic relationship established with the patient.

The *Pharmacist's Workup of Drug Therapy* (PWDT) is a tool available to practitioners that serves as a guide through the steps of the patient care process. It offers a standardized format for efficient documentation of patient-specific information needed for a financially viable pharmaceutical care practice.

Patient assessment

The practitioner begins by assessing the patient's understanding, expectations, concerns, and behaviors relative to drug therapy to determine if *drug-related needs* exist. Other subjective and objective information is also gathered from review of patient records and other sources. The pharmacist then interprets that information to ensure all current therapy is appropriate and to iden-

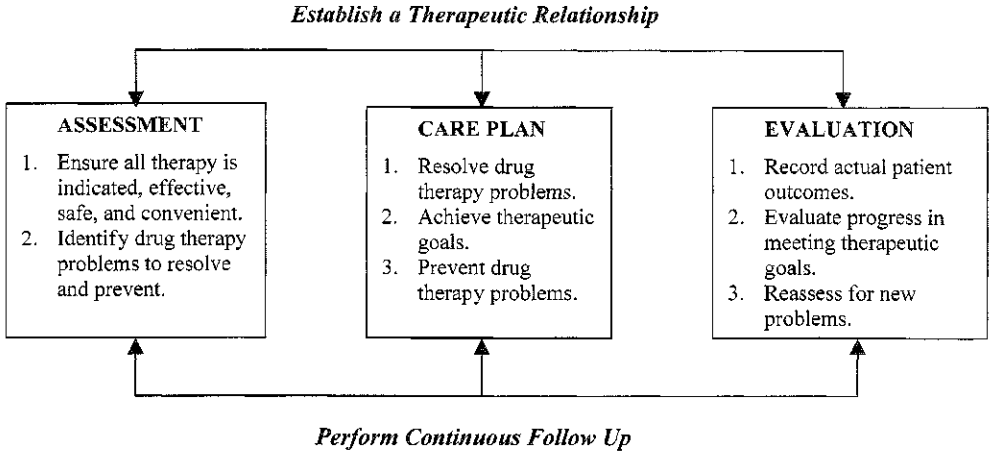

Fig. 1 The patient care process within a pharmaceutical care practice. Adapted from Cipolle, R.J.; Strand, L.M.; Morley, P.C. *Pharmaceutical Care Practice*; McGraw-Hill: New York, 1998, p. 129.

tify *drug therapy problems* that may be interfering with the goals of therapy or placing the patient at future risk.

A *drug therapy problem* is an undesirable event involving drug therapy that actually or potentially interferes with a desired patient outcome. Seven major types of drug-related problems have been identified that relate to the appropriateness, effectiveness, safety, and convenience of drug therapy (Table 1). There are multiple possible causes of each type of problem.

Drug therapy problems drive subsequent steps in the patient care process; therefore, they are stated clearly and with a high level of specificity. Moreover, they are prioritized according to their degree of urgency as determined by the severity of potential harm to the patient.

Pharmaceutical care plan

The purposes of a care plan are as follows: 1) to solve the existing drug therapy problems that were identified during the assessment; 2) to achieve the desired outcomes for each medical condition; and 3) to prevent the development of future drug therapy problems.

In creating a care plan, the practitioner:

- Specifies the desired therapeutic goal for each problem identified.
- Considers all feasible actions or choices that may be made to achieve the stated goals.
- Outlines interventions designed to resolve drug therapy problems.
- Designs a monitoring plan to assess effectiveness and minimize undesirable adverse effects of drug therapy.

These functions require ongoing collaboration with the patient and other clinicians to develop and implement a plan that is agreed upon and understood by everyone involved. The individual providing pharmaceutical care is then responsible for ensuring that optimal therapeutic outcomes are achieved.

Follow-up evaluation

The purposes of follow-up evaluations are as follows: 1) to determine the actual outcomes that were achieved by the plan; 2) to assess the extent to which the plan has achieved the desired outcomes; 3) to determine if there are new or changing drug therapy problems that must be addressed; and 4) to determine if anything has occurred that increases the patient's risk for developing new drug therapy problems. The patient's progress is documented accurately in the pharmacy record and communicated effectively to the patient and other health care providers.

The status of each medical condition can be described according the following categories:

- *Resolved*—the goals have been achieved and therapy is completed.
- *Stable*—the goals have been achieved, but continue the same therapy.
- *Improved*—progress is being made toward achievement of the goals, so continue the same therapy.
- *Partial improvement*—progress is being made, but minor adjustments in the therapy are required.
- *Unimproved*—there is no measurable progress yet, but continue the same therapy.
- *Worsened*—there is a decline in health, so revise the therapy accordingly.

Table 1 Relationship of drug-related needs to drug therapy problems

Drug-related needs	Drug therapy problems
Appropriate indication for drug therapy	1. *Need for additional drug therapy*: Patient has a medical condition that requires initiation of new or additional drug therapy.
	2. *Unnecessary drug therapy*: Patient is taking drug therapy that is not needed given their present medical condition.
Effective drug therapy	3. *Wrong drug*: Patient has medical problem treated with therapy that is less effective, more costly, or more hazardous than alternative therapies.
	4. *Dose too low*: Patient is taking correct drug for medical condition, but too little of drug is being taken.
Safe drug therapy	5. *Adverse drug reaction*: Patient has medical problem caused by an adverse drug effect, which may include a side effect as well as an allergic reaction; idiosyncratic reaction; and a drug–drug, drug–food, or drug–laboratory test interaction.[a]
	6. *Dose too high*: Patient is taking correct drug for medical condition, but too much of drug is being taken.
Convenient drug therapy	7. *Nonadherence*: Patient has medical problem resulting from not taking or receiving drug prescribed.

[a]In early descriptions of drug therapy problems, drug–drug, drug–food, and drug–laboratory test interactions were included as a separate eighth type of problem.

- *Failure*—the goals are not achievable with the present therapy, so initiate new therapy.
- *Expired*—the patient died while receiving drug therapy.

If changes in the plan are required to maintain or improve its efficacy, safety, or economy, the clinician coordinates these changes and communicates them to the patient and other health care providers.

Practice Management System

A practice management system provides the support necessary for effective and efficient practice. The system must allow for the addition of new patients and ensure the long-term financial viability of the practice. The system generally includes the following elements: 1) a statement of the mission of the practice; 2) the physical, financial, and human resources needed to support the practice; 3) a documentation system to evaluate the practice; and 4) reimbursement mechanisms to compensate the clinician and support the continuation of the practice.

MEASURING OUTCOMES OF PHARMACEUTICAL CARE PRACTICE

Cipolle and colleagues reported the outcomes achieved by 50 pharmacists who had completed the pharmaceutical care training program of the Peters Institute of Pharmaceutical Care at the University of Minnesota. Between 1993 and 1999, 14,357 patients received pharmaceutical care in 30 different ambulatory practice settings. The pharmacists assessed 97,511 drug therapy regimens and identified, resolved, and prevented 19,140 drug therapy problems. In a clinical and financial analysis of 1500 patients conducted between January 1998 and August 1999, pharmacist interventions avoided 193 unnecessary clinic visits, 72 multiple office visits, 36 emergency department visits, 28 urgent care visits, and 14 hospital admissions. Drug costs were reduced on 177 occasions. An estimated cost savings of $144,626 was realized, which reflects a savings of approximately $60 per patient. This represents a savings-to-cost ratio of 2:1 for the pharmaceutical care provided. When clinical outcomes of patients were evaluated, problems were resolved in 10%, stable in 38%, improved in 17%, and partially improved in 17%. Fourteen percent of patients were unimproved, 3% were worse, and 1% failed therapy. The authors concluded that the quality of care provided had a substantial positive impact on the clinical well-being of patients as well as on economic outcomes.

OBTAINING COMPENSATION FOR SERVICES PROVIDED

For a patient care practice to be recognized by the federal government and other third-party payers, four elements must be present: 1) a defined patient care practice;

2) a documentation system; 3) a formal evaluation system; and 4) reimbursement systems based on the level of patient needs.

Pharmacists participating in collaborative patient care environments (including disease state management and clinical pharmacy service programs) have experienced varying degrees of success in obtaining payment for the care provided. Although direct payment from patients is infrequently sought, a mail survey of 2500 American adults indicated that 56% of respondents were willing to pay for comprehensive pharmaceutical care services after they were provided with a description of what such care entailed.

Several different types of billing mechanisms have been used to gain compensation from third parties for services that are not tied directly to dispensing a drug product. Examples include fee-for-service, capitation payment, and the Health Care Financing Administration (HCFA) 1500 claim form. Each method has inherent advantages and disadvantages and may not be a suitable method for compensation for a comprehensive pharmaceutical care practice.

Payment for the majority of the patient care services provided by physician and nonphysician practitioners is based on the *resource-based relative value scale (RBRVS)*. The RBRVS ranks services according to the relative costs of the resources needed to provide them. The resulting relative value scale is then multiplied by a dollar figure to convert the service into a payment schedule. This payment model was successfully applied to pharmaceutical care practice in the Minnesota Pharmaceutical Care Project. Five levels of patient need were created based on the following: 1) the number of the patient's medical conditions; 2) the number of medications the patient is taking; and 3) the number of drug therapy problems identified. At 10 different community pharmacy practices in 1994, the average payment for a patient encounter was $12.14.

CHALLENGES TO IMPLEMENTATION OF PHARMACEUTICAL CARE

To date, actual and perceived barriers have impeded widespread acceptance and implementation of pharmaceutical care practice. Some factors affecting individual pharmacists include inadequate education and training in the required skills, absence of suitable role models and mentors, lack of time due to dispensing pressures, unwillingness to change to an entirely new philosophy of practice, fears of legal liability, fear of failure, and the absence of a tangible reward system. Pharmacy systems may pose impediments related to insufficient support personnel, lack of automated dispensing systems, limited physical facilities or poor organization of the available space, lack of adequate pharmacist compensation for cognitive functions, limited communication due to physical isolation from the patient and other health professionals, and inability to access necessary patient medical information. Other real or perceived barriers may include the resistance of physicians, administrators, and others; outdated and overly restrictive state board of pharmacy regulations; and lack of a market-driven demand for pharmaceutical care by the public.

CONCLUSION

Pharmaceutical care is a practice in which the clinician, working in concert with the patient and other health care providers, takes shared responsibility for the outcomes of all aspects of a patient's drug therapy. The goal of the practice is to ensure that every patient seen by the practitioner receives the most appropriate, effective, safe, economical, and convenient drug therapy possible. This is accomplished through the identification and resolution of actual and potential drug therapy problems. The essential components of a pharmaceutical care practice include a philosophy of practice, a patient care process, a documentation and evaluation system, and a method for obtaining financial compensation. All these elements must be in place for the practitioner to become recognized and compensated as a health care provider within the U.S. health care system. The future widespread adoption of pharmaceutical care practice by the pharmacy profession has great potential to reduce morbidity and mortality due to preventable drug therapy problems.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Linda M. Strand, PharmD, PhD, and Robert J. Cipolle, PharmD, for their thoughtful review of this article.

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Pharmaceutical Care Spain Foundation

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INTRODUCTION

In 1998, a group of Spanish community pharmacists created an organization to promote educational, scientific, and professional activities in pharmaceutical care. After several contacts and meetings, a nonprofit foundation was constituted in 1998 named the Pharmaceutical Care Spain Foundation and was established in Barcelona (Muntaner Street 560 pal 1ª, 08022 Barcelona, Spain; phone and fax: 0034-93-2113108; e-mail: vade1@nacom.es).

The aims of this Foundation are:

- To implement, promote, and develop pharmaceutical care in Spain and Latin American countries, according to the concept formulated by Hepler and Strand in 1990.[1]
- To support health institutions and researchers interested in pharmaceutical care, to achieve a high quality of the research projects.
- To promote research projects on pharmaceutical care.
- To offer educational programs and counseling on subjects related to pharmaceutical care.
- To spread the results of the research studies and progress on pharmaceutical care through the organization of congresses, courses, meetings, workshops, and publications.

The Foundation is constituted by patrons that can be individuals or institutions. Most individuals are pharmacists, but there are also some physicians. Among the institutions that are patrons of the Foundation are medical organizations such as the Academy of Medical Sciences of Catalonia and Balearic Islands (ACMCB); Spanish primary healthcare net (REAP); Group CESCA, a scientific organization of primary care; and the Gerontology International Foundation (FGI). The support of these medical societies is essential for the credibility and progress of pharmaceutical care practice.

The Foundation also has a growing number of "collaborators"—individual pharmacists who are interested in the objectives of the Foundation. The number of such collaborators is constantly growing—at the end of May 2001, it was 400.

WHY THE FOUNDATION WAS CREATED

In Spain, during the 1970s, some hospital pharmacists initiated an important change in hospital pharmacy practice. Pharmacists began to leave their pharmacies, to offer their knowledge to physicians and nurses in hospitals, to integrate themselves into the healthcare team, and to reorient their professional practice by having the patient as the center of their activity. This process became the introduction of clinical pharmacy practice in hospital pharmacies that later demonstrated its effectiveness by improving the quality of care as well as its economic efficiency.[2]

However, the concept and philosophy of clinical pharmacy is not yet implemented in all hospitals and is found even less among community pharmacists. Most community pharmacists saw clinical pharmacy linked to hospital practice and hardly adapted to the needs of the community practice setting. That is probably the reason why the pharmaceutical care concept was formulated by Hepler and Strand. But with the concept of pharmaceutical care, we carry the same risk as with clinical pharmacy. Many people are talking about the concept, but few are putting in the effort and means required to put it into practice.

Pharmaceutical Care Spain Foundation was created with the desire to influence the society in general—starting with the community of pharmacists—in order to disseminate pharmaceutical care practice to improve healthcare quality and to provide better service to the patients and to the healthcare system. Consequently, the Foundation has to extend pharmaceutical care practice among practitioners. The Foundation works with officially established pharmaceutical organizations in order to clarify the direction in which pharmacy practice should be oriented and to determine which services are offered to the citizens. These services have to go further than simply drug dispensing. The Foundation must also convince healthcare authorities that pharmaceutical care is adding a significant

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006384

value to the drug itself, making the prescription and use of drugs more rational and consequently more cost effective. Also, in relation to Spanish universities, the Foundation has to influence the reorientation of its educational programs and teaching methods in order to create the culture, attitudes, knowledge, and skills required among pharmacy students to provide pharmaceutical care to society. Pharmaceutical care should be the main educational objective for all schools of pharmacy. Finally, another reason for the Foundation is the need to inform and to show the benefits that people can obtain from the pharmaceutical care practice in terms of ensuring the safety and effectiveness of their pharmacotherapy. No service will be demanded by society if people ignore its existence and the benefits that can be obtained from it.

ACTIONS OF PHARMACEUTICAL CARE SPAIN FOUNDATION

In two years of existence, the Foundation has developed some activities in order to achieve the abovementioned objectives:

- *Journal Pharmaceutical Care Spain*: This publication was initiated in January 1999,[3] with six issues per year. The contents of the journal are original papers, reviews, international news, drug information, etc. Also, a continuing education program is offered through the journal to all subscribers.
- Vade mecum of the official technical information about drugs commercialized in Spain: this is offered via the Internet to all physicians and pharmacists of the country through the Web at www.saludaliafarma.com or www.saludaliamedica.com.
- Procedures manual on pharmaceutical care: Because many colleagues plan to initiate provision of pharmaceutical care but do not know how to start, the Foundation published this manual to guide them.[4]
- First National Congress of Pharmaceutical Care: Held in San Sebastián with more than 1000 participants, this congress included several distinguished speakers, including Charles Hepler, Linda Strand, J.W. Foppe van Mil, and Robert Cipolle. The Ministry of Health also attended the meeting and 77 communications on Pharmaceutical Care experiences were presented.
- Consensus on pharmaceutical care: Due to the differing conceptions that Spanish professional groups have on pharmaceutical care, and the difficulties in translating English terminology into Spanish, a working party with all the interested groups was established in order to achieve a consensus document on the subject. This working group had been coordinated by the General Director of Pharmacy of the Ministry of health.[5]
- Competencies document: A competencies document of the pharmacy profession is planned with strong participation by the Pharmaceutical Care Spain Foundation. The document is intended to define the areas in which pharmacists are competent within the healthcare practice.[6]

RECENT AND FUTURE DEVELOPMENTS

During 2001, the Foundation offered different courses through the Internet. Topics include:

- Methodology to implement pharmaceutical care into practice.
- Concepts on pharmacoepidemiology.
- Pharmacoeconomics.
- Evaluation of the scientific biomedical literature.

Other courses will be more oriented to pharmacotherapy:

- Treatment of blood coagulation disorders.
- Arterial hypertension.
- Peripheral vascular pathologies.
- Congestive heart failure.

The Foundation held the Second National Congress on Pharmaceutical Care November 2001 in Barcelona. The main subject of this congress was "communication with patients and with the other healthcare practitioners." The Foundation believes that communication skills are the main deficiencies of community pharmacists, and these are essential for pharmaceutical care implementation and practice.[7]

Some research projects promoted or initiated by the Foundation are currently ongoing. A European research consortium, with the participation of different countries, is proposed to study the influence of pharmaceutical care in the control and treatment of minor diseases from community pharmacists, and it has submitted to the European Community in Brussels asking for economic support. Such research will be coordinated by the School of Pharmacy of the University of Manchester, United Kingdom. A project promoted by the European Society of Clinical Pharmacy is currently studying the number of drug related problems (DRP) identified by community pharmacists on patients discharged from the hospital. A research study on the number of DRP identified by pharmacists in patients admitted to emergency services of hospitals was initiated

to find out how many patients are admitted in emergency rooms because they are suffering some DRP, and how many of these DRPs could be prevented through pharmaceutical care practice.

The Pharmaceutical Care Spain Foundation is also cooperating in an organization called Pharmaceutical Care Network Europe (PCNE) that is promoting pharmaceutical care practice and research. One of the difficulties we have in Europe is the diversity of pharmacy organization system and practice, as well as languages and healthcare structure. Such differences, between European countries, are well discussed by Foppe van Mil.[8]

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Pharmaceutical Outcomes

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INTRODUCTION

Pharmaceuticals are among the most widely used interventions in health care today. They are used in both the prevention and treatment of disease and amelioration of symptoms to improve patient outcomes. The relative importance of pharmaceuticals in health care is growing in most industrialized nations, as the percentage of health care expenditures for pharmaceuticals continues to increase. Spending on prescription drugs in the United States is increasing at a rate of 12% annually and will continue to increase approximately 10% per year over the next 8 years.[1]

Not all outcomes from the use of pharmaceuticals are positive. Adverse drug reactions are the fourth to sixth leading cause of death,[2] and in the United States, medication errors are the largest category of the 44,000–98,000 deaths each year due to medical errors.[3] The total annual cost of drug-related morbidity and mortality in the ambulatory setting in the United States has more than doubled in 5 years, increasing from $76.7 billion in 1995 to $177.4 billion in 2000.[4]

Many drug-related adverse outcomes are preventable. For example, a significant percentage of hospital admissions are due to drug-related morbidity,[5] and approximately one-half of these admissions are preventable.[6,7] Preventable adverse outcomes related to drug use—often referred to as preventable drug-related morbidities (PDRMs)—are typically not due to the inherent pharmacological properties of medicines, but rather to problems such as a lack of systematic approach to monitoring of patients receiving drug therapy by health professionals. A Canadian study estimated that the annual cost of PDRM in older adults in that country is $10.9 billion (Canadian) CND.[8]

One framework for looking at pharmaceutical outcomes—whether these outcomes are positive or negative—is the ECHO (Economic, Clinical, and Humanistic Outcomes) model, proposed by Kozma, Reeder and Schulz.[9] According to this model, three main types of health-related outcomes should be considered: economic (drug-related and non-drug-related), clinical (clinical events, physiologic and metabolic measures), and humanistic outcomes [such as patient satisfaction and health-related quality of life (HRQoL)].[9] Economic and clinical (and fairly often humanistic) outcomes are incorporated into pharmacoeconomic evaluations.

Patient satisfaction is growing in importance and has become a key part of most health care report cards. Perceived satisfaction with medical treatment is key in determining the overall well-being and health of patients, and is recognized as being one of the main components of quality. HRQoL relates to those aspects of a patient's life dominated by personal health. Although differing opinions exist, there is some consensus that there are four main dimensions (or domains) constituting "health": a physical dimension, a functional dimension, a psychological dimension, and a social dimension.[10] Increasingly, HRQoL is being used in clinical drug trials and in pharmacy program evaluations, and to monitor patients.[10]

Although this article focuses on pharmaceutical outcomes, it is worth noting the relationship of outcomes to processes and structures. Donabedian has argued that understanding health care structures, process, and outcomes is critical.[11] Structure and process performance measures are commonly used by health care organizations. However, they are of limited value because few structures and processes have been proven to be directly associated with patient outcomes.[12] Still, an understanding of processes, and even structures, is important to improve the efficiency of health care services.[13] Lipowski recommends that outcomes be evaluated first and then processes, but cautions that determining a definite causal relationship between the two is often difficult.[14] Monitoring process and outcomes are interrelated activities.[15–18] Improving outcomes is the goal; studying processes can point the way to achieving that goal, and outcomes must be linked to processes to improve the quality of health care.[19] Global outcomes such as

morbidity and readmission are the results of multiple factors, and it is difficult to attribute those outcomes to a specific encounter or element of care without additional information about key factors.[16,20–22] Although outcome studies are increasingly being undertaken, there is much to be learned about the relationships between processes and outcomes.

EVALUATING PHARMACEUTICAL OUTCOMES

Misuse, underuse, and overuse of medical care and pharmaceuticals can lead to suboptimal patient outcomes. These are severe problems that require urgent attention.[19] Indeed, measurement of quality of medical care is a daunting but essential task.[23] Most organizations such as pharmacy regulatory agencies and hospitals, which evaluate the medication use process, focus on structural elements (such as checking whether narcotics are safe and secure, and whether pharmacists' licenses are displayed) that have questionable relationships to patient outcomes. However, the evaluation of pharmaceutical-related patient outcomes is becoming more important as employers and health care payers are demanding more accountability and transparency with health care spending.

Performance Measures

Performance measures, or indicators, are frequently used to measure and compare pharmaceutical outcomes. Performance measures are used to monitor and evaluate important governance, management, clinical, and support functions that affect patient outcomes.[24] A performance measure can be used in one of three ways: to warn of potential quality problems, to measure the result of process improvement, and to monitor continuing performance.[25] They are typically expressed as ratios.

These measures can define practice norms when absolute standards or the prevalence of conditions and practices are unknown. Findings can be compared over time and space, across sites of care and health care organizations. Patterns, trends, and gross variation from practice norms are discernible.

The two major types of performance measures are: 1) rate-based performance measures, which measure an event for which a certain proportion of the events are expected to occur even with quality care (such as mistimed prescription refills); and 2) sentinel-event performance measures, which measure a serious event that requires an indepth review for each occurrence of the event (such as a medication error).[24] To provide meaningful information, performance measures must be reliable, valid, and feasible. To ensure this, they must be carefully selected, thoroughly tested, evaluated, and used within the context of a comprehensive performance measurement system.[26] In isolation, no single measure serves as a direct measure of quality but as an indicator of the need to direct attention to a potential problem.

Performance Measurement Systems

Some of the more common performance measurement systems used to assess pharmaceutical outcomes include report cards, balanced scorecards, clinical value compasses, profiling, performance-based evaluation systems, and others. The goals of pharmaceutical performance measurement systems are to: 1) compare treatment modalities fairly; 2) recognize and promote good care; 3) identify and eliminate substandard care; and 4) improve the level of care overall.[27] Because performance measures can include data over the course of treatment, the outcomes of alternative therapies and practices may be detected. The end goal of any performance measurement system should not be cost containment only; improving patient outcomes must be a primary concern, keeping in mind the cost effectiveness of the therapy and sustainability of the system.

All performance measurement systems must consider the level of outcomes data collection and aggregation. Assessment can occur at multiple levels: by individual practitioner, institution, geographic region or state/province; by symptoms, diseases, or organ system; by encounter, episode of care, or continuous monitoring; and by the setting or settings in which care was delivered. The size of the population will affect the level of aggregation that is reasonable. Large samples are required to detect differences in processes and outcomes of care. Moreover, the time span covered by the data in conjunction with the size of the population will determine the level of aggregation possible.

Uses of Performance Measurement Systems

A survey of stakeholders of provider profiling of pharmaceutical use in the United States revealed that the top five uses for these systems are (in descending order of use): 1) educate and give information to the physician; 2) change physician behavior and influence prescribing patterns; 3) monitor and improve the quality of care; 4) identify potential problems; and 5) improve patient outcomes.[28] A Canadian survey had similar results.[29]

Performance measures can reveal the impact of provider practice patterns on medical care, resource use, and cost of care. Often, this information is provided back

to the physician or other health care practitioner so the individual can review their own data. Indeed, when interventions have shown positive changes in medical practice, one consistent finding is that providers were given information on how their practices and outcomes compared with others in the community.[30,31] Feedback is successful when used alone or in combination with education, rewards, or the support of opinion leaders.

Pharmaceutical outcome data are also used to improve the quality of care, identify potential problems, and improve patient outcomes. These data are often used within a continuous quality improvement (CQI) cycle, where rate-based performance measures are tracked over time and used in conjunction with control charts to show changes in quality and assess the impact of programs or changes in process. Information can be fed back to front line health care practitioners, areas for possible improvement identified, appropriate changes made, and reassessments initiated.

Examples of Specific Performance Measurement Systems

The United States has several major performance measurement systems in place. Two of the most important systems are those directed by the National Committee for Quality Assurance (NCQA) for managed care organization (MCO) accreditation and The Joint Commission on Accreditation in Healthcare Organizations (JCAHO) for health care organization accreditation. Both NCQA's performance measurement system, HEDIS, and JCAHO's IMSystem include several pharmaceutical outcomes indicators.

Several other projects in the United States are developing further pharmaceutical outcome measures. SCRIPT (Study of Clinically Relevant Indicators for Pharmacologic Therapy), initiated by the Health Care Financing Administration (HCFA), is a multidisciplinary coalition representing 52 public and private sector organizations that is currently beta-testing several pharmaceutical performance measures.[32] The Performance Indicators for Continuous Quality Improvement in Pharmacy (PICQIP) study, a partnership between the University of Florida and the American Pharmaceutical Association Foundation Quality Center, is an example of new pharmacy indicators being used in a CQI cycle.[33,34]

The Canadian Institute for Health Information (CIHI) is actively working on developing drug performance indicators for uptake and application by the Canadian Council on Health Services Accreditation (CCHSA). In Great Britain, the National Health Service (NHS) has established a National Performance Framework that has developed primarily process indicators to assess the impact of health services. The National Prescribing Service (NPS) was launched by the Australian Government in 1998 and is undertaking work in Quality Use of Medicines (QUM). It has also done work in the area of measurement of pharmaceutical outcomes.

Limitations of Evaluating Pharmaceutical Outcomes

David Eddy at Duke University has written extensively on the problems and potential solutions related to pharmaceutical performance measurement systems.[22] According to a U.S. survey, the most commonly perceived problems with pharmaceutical performance measurement systems are limitations with billing and administrative databases, lack of time to review summary data by physicians, and incomplete data.[28] Other limitations include risk adjustment (what if my practice has "sicker" patients), overreliance on administrative (claims) data rather than clinical data (therefore lacking key patient outcomes), patient individuality and variation in medical practice, and lack of capacity for taking into account a discipline-specific rather than a whole programs-oriented CQI approach. There has also been some debate on the reliability of performance measurement systems to assess the true impact of physician care on the quality of health care.[35,36]

DATABASES FOR PHARMACEUTICAL OUTCOMES

Difficulty in obtaining the data necessary for measurement hinders pharmaceutical outcomes assessment. Both clinical and administrative data sources have limitations. Medical chart review is time consuming and expensive, and not all findings and services rendered by providers are documented faithfully.[37] Administrative records, often in the form of paid claims for reimbursement, are more readily retrievable, but are collected for administrative purposes and need validation to be used for assessing pharmaceutical outcomes.

Available sources from the public system include census data, health expenditure data, physician clinical record billing data, prescription drug claims data, population health surveys, hospital and nursing home medical records, and disease- or organ-specific registries. Private sector data include data from the pharmaceutical industry, private insurance industry, drug benefit management companies, and individual private firms.[38] Developments in health care information technology (IT) should

facilitate the collection of pharmaceutical outcomes data in the future.

ETHICS, PRIVACY, CONFIDENTIALITY, AND DATA SECURITY

It is generally accepted that persons have a right to control their health information so they are not harmed. Many jurisdictions are developing guidelines or legislation related to privacy, confidentiality, and security of personal health information. For example, in the United States, the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and the associated final Privacy Rule of December 28, 2000 (which took effect on April 14, 2001) gave patients more control over how their personal health information is used, and addressed the duties of health care plans and providers to protect health information.[39] Research ethics committees need to determine when patients need to give explicit consent for the use of their personal health information for new research questions when it has been collected for other research questions or administrative purposes. The soundness of scientific methodology needs to be assured. The potential public health benefit of the research needs to be weighed against any risk to the individual. Guidelines for data confidentiality and anonymity have been developed in many jurisdictions and methods for masking or delinking personal identifiers or reporting only aggregate data have been developed and implemented. Conflict of interest and financial relationships in the research need to be disclosed. There should also be vigilance on the technical side of ensuring security of data including controlled access to and storage, maintenance and transmission of, personal health information.[40–46]

ROLE OF VARIOUS STAKEHOLDERS IN PHARMACEUTICAL OUTCOMES MEASUREMENT

Improving drug use outcomes requires the participation and cooperation of everyone involved in the case process. Physicians and other prescribers should specify the therapeutic objective in writing for each prescription they write, and this should be communicated to the patient and other members of the health care team. Pharmacists, nurses, and other health care professionals should monitor patients, documenting their interactions with patients, and communicate this information back to the health care team. ASHP's Statement on the Pharmacist's Role in Primary Care advocates the measurement of pharmaceutical care outcomes: "High-quality, coordinated, and continuous medication management for patients should be measurable as a result of the provision of pharmaceutical care within a primary care delivery model," and "Pharmacists should evaluate all components of the medication-use process to optimize the potential for positive patient outcomes."[47] Health administrators need to implement systematic ways of measuring the processes, outcomes, and costs of medication use. Health policy makers should take note of policy synthesis documents, evidence of the effectiveness of drug policies implemented in other jurisdictions and, when possible, evaluate policies and programs to determine their effect on patient outcomes, health care resource utilization and costs. Pharmaceutical companies need to help health practitioners proactively identify patients at risk for PDRM from their products and help to implement systems to improve drug use. They need to continue to participate in methodologically sound pharmaceutical outcomes research. Finally, each time they receive a prescription, patients should question what is the intended outcome of this drug and who will be working with me to ensure that I achieve this outcome?

USEFUL RESOURCES

Textbooks

International Society for Pharmacoeconomics and Outcomes Research, ISPOR Lexicon Pashos, Klein, Wanke, L.A., Eds.; ISPOR: New Jersey, 1998.

Spilker, B. In Quality of Life and Pharmacoeconomics in Clinical Trials; 2nd Ed.; Spilker, B., Eds.; Lippincott-Raven: Philadelphia, PA, 1996.

Organizations/Web Sites

Academy of Managed Care Pharmacy (www.amcp.org).

American College of Clinical Pharmacy (Outcomes and Economics PRN) (www.accp.com).

Academy for Health Services Research and Health Policy (www.academyhealth.org).

Canadian Coordinating Office for Health Technology Assessment (www.ccohta.ca).

International Health Economics Association (www.healtheconomics.org).

International Society for Pharmacoeconomics and Outcomes Research (www.ispor.org).

International Society for Pharmacoepidemiology (www.pharmacoepi.org).

International Society for Quality of Life Research (www.isoqol.org).
National Committee for Quality Assurance (www.ncqa.org).
Society for Medical Decision Making (www.smdm.org).

ACKNOWLEDGMENTS

The authors acknowledge the contributions of Sharon Boriel, Susan Bowles, Murray Brown, Chole Campbell, and Rick Manuel.

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Pharmaciens Sans Frontières (Pharmacists without Borders)

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INTRODUCTION

Pharmaciens Sans Frontières is a humanitarian nongovernmental organization conducting emergency and development missions in medically underprivileged countries. Its contributions range from the provision of essential drugs and medicosurgical supplies to the renovation of healthcare facilities and the education of resident healthcare professionals.

GOAL

Pharmaciens Sans Frontières (PSF) strives to promote and establish economical and geographical access to quality healthcare for all, through adapted pharmaceutical means.

OBJECTIVES

Pharmaciens Sans Frontières is pursuing the following objectives:

- To analyze and itemize the hygiene and public health (sanitary) needs of populations.
- To provide selected drugs and medicosurgical supplies to recipient countries.
- To ascertain the best supplying strategies for a prompt, careful, and secure delivery of goods.
- To support the establishment of community clinics, hospitals, and public pharmacies in collaboration with local authorities, international institutions, and other nongovernmental organizations.
- To give technical assistance and train resident staff working in pharmaceutical facilities.
- To enhance drug knowledge of resident healthcare professionals by providing information material, organizing educational programs, and encouraging professional associations and committees.
- To promote rational drug use through training programs and public education campaigns.
- To collaborate with health care professionals from other humanitarian agencies.
- To apply pharmaceutical expertise to the safe management of healthcare waste.

HISTORY

Pharmaciens Sans Frontières was founded in 1985 by five French pharmacists: Philippe Bon, Michel Camus, Jean-Louis Machuron, Bernard Toureet, and Daniel Tsantucci. The original ambition was to collect unused drugs, then to sort and distribute those still valid to the most disadvantaged nations of the world. Through this first initiative, the pharmaceutical profession secured its legitimacy within the field of humanitarian aid. From the outset, PSF's action was aimed at improving the sanitary situation of developing countries. In 1987, the first interventions commenced in Mali and in Mauritania.

These early efforts highlighted the unsuitability of unused drugs for the needs of medically underprivileged countries. Since then, the World Health Organization has issued guidelines for drug donations (www.drugdonations.org) and a list of essential drugs (www.who.int/medicines/edl.html) endorsed by PSF. Intended to meet the needs and resources of third world and developing countries, the list of essential drugs is used to guide purchasing decisions and procurement schemes both during acute emergencies and development aid. PSF then created a wholesaler for the provision of essential drugs, medicosurgical supplies and biological substances.

In late 1989, PSF had acquired the necessary credibility with French and European authorities to establish an emergency mission in Romania. Soon after, programs of a similar magnitude were launched in Burkina Faso and in Bulgaria.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006302

The number of missions has continued to grow since 1992. The association conducts programs in all facets of the pharmaceutical profession, namely goods distribution, management, training, technical assistance, and facility renovation. Consequently, PSF's organizational structure has expanded markedly. An International Committee has been formed that currently includes Belgium, Canada, France, Italy, Luxembourg, the Netherlands, Poland, and Switzerland. Through its sustained efforts, PSF has now gained worldwide recognition.

MISSIONS

Pharmaciens Sans Frontières administers three different types of international missions: emergency, development, and technical assistance.

Emergency Missions

During these missions, PSF supplies drugs and medicosurgical materials to countries afflicted by natural, economic, or human catastrophes. These interventions are rapidly launched to respond to a critical situation. Soon after, a postemergency program should be planned in order to extend the aid beyond the initial punctual contribution.

Development Missions

These missions foster the health care autonomy of populations through more long-term aid. They result in establishing village pharmacies and in renovating hospital facilities and medical laboratories.

Technical Assistance Missions

When the situation is favorable, missions can be accomplished that involve expertise and training and affect the whole pharmaceutical field. Examples of such missions include restoration of industrial drug production capabilities and reinstatement of a national laboratory for drug quality control with subsequent training of technicians.

Current Missions

Pharmaciens Sans Frontières is currently operating an emergency mission in Tadjikistan and development or technical assistance missions in the following countries: Albania, Bosnia, Cambodia, Equator, Honduras, Kenya, Kosovo, Mali, Mauritania, Moldovia, Montenegro, Niger, Serbia, and Soudan.

FUNDING

Like all nongovernmental organizations, PSF relies on two sources of funding: institutional sponsors and private contributions. These funds ensure the self-reliance of the association.

Institutional Sponsors

Whether from the European Union, the United Nations High Commissioner for Refugees, the French Ministry of Foreign Affairs, or the United States Agency for International Development, these funds are intended exclusively for the establishment or the continuation of missions in the field. Granting of these funds entails a detailed application, following the assessment of the pharmaceutical needs in a given region or country, and a thorough account at the completion of the program. Most funds make provision for administrative charges, which partially cover the operating cost of these programs.

Private Contributions

Donations, subscriptions, and industry partnerships mainly serve to fund development missions, transitional programs between emergency and development missions, logistic material not otherwise covered by the institutional sponsors, and the operations of the association.

Financial Transparency

Close to 90% of the funds are earmarked for the carrying out and direct management of missions in the field. In order to assure transparency, PSF's finances are controlled by independent agents and are stratified by mission.

HUMAN RESOURCES

Board of Directors

The Board is formed of approximately 20 volunteer directors, elected by the members of the association. Claudi M. Cuchillo currently serves as President.

Staff

Some 30 employees work at the international headquarters in Clermont-Ferrand and at the marketing office in Paris, France. The key managers are as follows:

- Executive Director: Gérard Plantin
- Director of Finance: Raphaël Chaize
- Director of Human Resources: Gérard Pourreaux
- Chief of Marketing: Isabelle Leroi
- Chief of Accounting: Françoise Chargueraud
- Communication Officer: Samuel Falgoux

National Associations

- PSF Belgium: Mrs. Solange Gossieaux, Forêt d'Houthulst 27, 1000 Brussels, Belgium.
- PSF Canada: Mr. Hubert Brault, a/s A.Q.P.P, 4378 Pierre de Coubertin, Montreal, Qc, Canada H1V 1A6.
- PSF Netherlands: Mr. Tammes, Apothekers Zonder Grenzen, PO Box 10493, 7301 GL Apeldoorn, Netherlands.
- PSF Italia: Mrs. Elena Gandini, Farm- Piazza Vittorio Emanuele III no. 4, Monzambano, Italia.
- PSF Luxembourg: Mr. Camille Groos, 13 G. Diderich, 1420 Luxembourg.
- PSF Poland: Mr. Zygmund Ryznerski, Farmaceuci Bez Granic, 2 PL W. Slkorslkiego, 31115 Krakow, Poland.
- PSF Switzerland: Mr. Pierre Alain Jotterand, Route de Crochy 2, Case Postale 229, 1024 Ecublens, Switzerland.

Missionaries

Over 1000 volunteers are presently members of PSF around the world. At any point in time, between 90 to 100 expatriated of diverse nationalities and trades (such as pharmacists, technicians, nurses, logisticians, and administrators) and some 400 local staff combine forces to improve health care in the field.

MEETING

The annual general meeting of the members is held in May.

PROFESSIONAL DEVELOPMENT

Pharmacist Managed Vaccination Programs

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INTRODUCTION

In the United States, the concept of pharmacists as vaccine providers is new; however, a small number of pharmacists have been administering vaccines for decades. Pharmaceutical care initiatives, spearheaded by state and national pharmacy organizations, have rapidly expanded the number of pharmacists who are qualified to administer vaccines. Based on the increased number of certificate programs offered each year, pharmacists are expanding their role in the health of American citizens by administering vaccines. The role of vaccine prescriber and provider is also new to school of pharmacy curricula and continues the expansion of community and institutional practitioners providing pharmacy-based clinical services. If embraced, pharmacist-managed vaccination programs will enhance other clinical services (e.g., diabetes pharmaceutical care) by providing one-stop shopping for basic disease state prevention and management services.

CERTIFICATE PROGRAMS

Pharmacists must be trained to provide and administer immunizations to their patients. The principle method of training has been through the development of immunization certificate programs. The first formal certificate program for pharmacists as providers of immunization services occurred in the state of Washington in 1994.[1] The American Pharmaceutical Association (APhA) organized a national Pharmacy-Based Immunization Delivery program that was first offered to Mississippi pharmacists in 1996. State pharmacy associations, many in conjunction with APhA and other national pharmacy associations, have sponsored live educational programs to help encourage and train interested pharmacists.[2] Since the mid-1990s, thousands of pharmacists have received specialized knowledge and training to appropriately select and administer vaccines through the completion of various certificate programs in eight states: Alabama, Arkansas, Iowa, Michigan, Mississippi, Texas, Tennessee, and Washington.[3] Once successfully completed, this credential indicates that a pharmacist has achieved a high level of competence in the field of immunizations. Twenty-four other states allow pharmacists to administer drugs; thus, the potential exists for pharmacists in these states with their current pharmacy practice acts, or slightly amended ones, to establish pharmacy-based immunization delivery services. If you are not sure about your state pharmacy practice act, call your board of pharmacy and ask if your state's practice act includes wording that allows for pharmacists to administer medications.

BENEFITS OF PHARMACISTS ADMINISTERING VACCINES

With each passing year, pharmacists are becoming more involved in the development of immunization programs and are accepting additional responsibilities by becoming active immunizers. The presence of pharmacists in most communities highlights the immense potential for the development of immunization programs. Although these opportunities are exciting for pharmacists, there are larger issues that are positively affected by these opportunities. In conjunction with physicians, nurses, public health clinics, and others, pharmacists fill a unique role for all those attempting to increase immunization rates. Compared with all other health care professionals, pharmacists are consistently more accessible in most geographic areas and have been regarded by the public as one of the most respected professions for more than 20 years. Most physicians and other health professionals in their local area see the emergence of this service as a positive development. Although there will always be some tension regarding such turf issues, the overall benefit of increasing the immunization rates nationally and decreasing morbidity and mortality far outweigh them.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006240

Health Economic Benefits

Vaccine administration is economically beneficial. Several studies have demonstrated the cost effectiveness of various vaccines. One study suggested that advising 100,000 at-risk patients to accept influenza vaccine would increase the number of vaccinations and could avert 139 hospitalizations and 63 deaths.[4] A study in the Journal of the American Medical Association analyzed pneumococcal vaccination of people 65 years of age and older, and when their findings were extrapolated to 23 million senior citizens, immunizing this population would save $194 million and gain 78,000 years of healthy life.[5]

With the addition of pharmacists to the role of immunizer, the immunization rate continues to increase. The public health benefits, as well as the professional opportunities for practitioners, increase. As patients become accustomed to receiving immunizations from their local pharmacist, the opportunities to develop other patient care services, such as disease management programs, increases significantly because patients become more comfortable with pharmacists in a clinical role.

Pharmacists have provided a needed boost in advocating the importance of vaccinations. Beginning in the early 1980s, pharmacists began to get more involved in vaccine advocacy by hosting influenza immunization teams at their pharmacies, evolving to present-day efforts that entail pharmacists in various practice settings—independent, chain, institutional, and consulting—actually administering immunizations.[6] Over this period of time, the addition of pharmacists to the campaign increased immunizations in all settings, including physicians' offices and pharmacies. With the development of pharmacist-managed vaccination programs, pharmacies have also experienced an increased patient traffic. Overall, the development of pharmacist-managed vaccination programs has demonstrated that participants—patients, other health care professionals, pharmacists, and society—benefit greatly from these programs.

Profit

Pharmacist-managed vaccination programs should be viewed as revenue generators, not necessarily as a profit center. According to the *2001 NCPA-Pharmacia Digest*, responding independent pharmacists that offer immunizations in their practices reported that, on average, 79% charged a separate fee for the service.[7] It is unlikely that any pharmacist will be able to make a living exclusively administering vaccines, but this service would be a good way to begin or expand clinical services. Even the most prolific pharmacist-immunizers have only been reimbursed $5000 to $10,000 per year. Immunizing is a way to get closer to clients as well as increase the status, in their eyes, of a pharmacist as a caregiver. In furthering one's status as a caregiver, one would expect an increase in spin-off business. For example, the client comes in for an influenza vaccine and while there the client takes the opportunity to ask the pharmacist's recommendation on purchasing an over-the-counter product.

IMMUNIZATION OPPORTUNITIES FOR PHARMACISTS

Pediatrics

Infant and childhood immunization opportunities abound, but many practitioners shy away from this practice because of liability concerns and because of being inexperienced at injecting infants and small children. If one can overcome these challenges, there are federally and state-funded programs designed to encourage adherence to complex pediatric vaccination regimens and to reimburse qualified clinicians providing these services.[8] The most widely recognized programs include the Vaccines For Children (VFC) program, and state-operated low-cost or free health insurance for children (e.g., Children's Health Insurance Program [CHIP], KidCare programs). One of the many services covered by most state children's health insurance programs includes immunizations, whereas the VFC was designed exclusively to, "provide FREE vaccine to children between the ages of birth and 18 years"[9] (Table 1).

Qualifications for the VFC program are as stated here. Each state's children's health insurance qualifications are unique but can be found at their web site.[10] Children through 18 years of age qualify to receive federally purchased vaccines under the VFC program if they are medicaid-enrolled, uninsured, or Native Americans/Native Alaskans. Children who have insurance that does not cover immunizations also qualify to receive VFC vaccine at federally qualified health centers and rural health clinics. In addition, states may use their funds to purchase vaccines for additional groups of children. Contact the immunization program in your state for more information.

Adult

Pharmacists certified to administer vaccines typically begin their clinical practices by immunizing adults against influenza and pneumococcal pneumonia. This

Table 1 Vaccines covered by Vaccines for Children program

Vaccine name(s): Common (brand)	Disease(s) prevented	Required for K–12 in most states
DTaP (Tripedia®, etc.)	Diphtheria, tetanus, whooping cough	Yes
Hib (PedvaxHIB®, etc.)	Haemophilus influenzae type b	No, DC
Hepatitis A (Havrix®, VAQTA®)	Hepatitis A	No
Hepatitis B (Recombivax HB®, Engerix-B®)	Hepatitis B	Yes
Flu (Fluogen®, etc.)	Influenza	No
MMR (M-M-R® II)	Measles, mumps, and rubella	Yes
Pneumonia (Pneumovax®, Pnu-Imune® 23)	Pneumococcal diseases	No
Pneumococcal conjugate vaccine (Prevnar®)	Infant pneumococcal	No
Poliovirus (IPOL®)	Paralytic poliomyelitis	Yes
Varicella (Varivax®)	Chicken pox	No

Key: DC, day care; DTaP, diphtheria, tetanus, and acellular pertussis; Hib, haemophilus influenza type b; MMR, measles, mumps and rubella.

broad population and these vaccines target the most undervaccinated population and can affect the two most vaccine preventable diseases in the United States. Combined, these two diseases kill between 50,000 and 80,000 people per year. Other vaccine-preventable diseases that are common in adult populations include hepatitis B, hepatitis A, and varicella.[11] Unlike the vaccines for influenza and pneumococcal pneumonia, these other diseases require multiple doses and the vaccines cost $25 to $60 or more per dose.[12] Yet another vaccine that many are not given because providers simply forget to offer it to their clients is the tetanus/diphtheria vaccine or Td. This vaccine requires a booster every 10 years after the age of 11 or 12.[13]

Elderly/Long-Term Care

The elderly suffer most in terms of increased morbidity and mortality when recommended vaccines are not administered. Pneumococcal diseases are the vaccine preventable diseases that cause, by far, the most mortality in the elderly.[14] Unfortunately, the vaccine for pneumococcal-induced pneumonia has one of the lowest administration rates. Other vaccines that most elderly and long-term care residents should receive include the influenza and tetanus/diphtheria vaccines. Consultant pharmacists or pharmacists providing services to long-term care facilities are in excellent positions to identify those who need vaccines.[15]

MODEL PHARMACIST-MANAGED PRACTICES

There are a number of opportunities for pharmacists to develop an immunization service in their current practice. However, the degree of development for a vaccination program depends on numerous factors, including, but not limited to, location of the pharmacy (both the state in which the pharmacy exists, as well as the physical location in the community), staff size, physical layout of the pharmacy, and other community health professionals currently involved in vaccinations (i.e., physicians, nurse practitioners, nurses, state health departments). Based on guidelines approved by the APhA Board of Trustees in 1997, there are three levels of involvement for pharmacists in vaccine advocacy:

1. Pharmacist as educator (motivating people to be immunized).
2. Pharmacist as facilitator (hosting others who immunize).
3. Pharmacist as immunizer (providing and administering immunizations).[16]

A logical role for all pharmacists is in the area of educating the public about the benefits and importance of immunizations. Pharmacists regularly speak at local civic, service, and school organization meetings to discuss health-related issues, and these serve as ideal settings to speak about the importance of immunizations. By keeping individual patient profiles, pharmacists also have a unique opportunity to identify and directly inform patients with special needs, such as those with a high risk of infection and the elderly, about the importance of receiving their pneumococcal and annual influenza immunizations. Vast amounts of educational material are available from local, state, and national organizations to aid in educating children and adults (see Table 2 for specific contact information). All pharmacists should meet this level of advocacy.

In daily dealings with physicians, nurses, insurance companies, and patients, the role of facilitator is com-

Table 2 Internet-based vaccine and immunization resources

Resource	Web address
AAP	http://www.aap.org/family/parents/immunize.htm
ACIP publications	http://www.cdc.gov/nip/publications/acip-list.htm
Adobe Acrobat Reader	http://www.adobe.com/products/acrobat/readstep2.html
CDC	www.cdc.gov
FDA web site for biological products	http://www.fda.gov/cber/efoi/approve.htm
Immunization Gateway: Your Vaccine Fact-Finder	http://www.immunofacts.com
Medicare Part B	http://www.medicare.gov/Basics/PartAandB.asp
Minnesota Dept. of Health phone numbers for vaccine companies	http://www.health.state.mn.us/divs/dpc/adps/manual/pgphonef/pgvacmfg.htm
MMWR	http://www.cdc.gov/mmwr
State health insurance programs for children	http://www.insurekidsnow.gov/childhealth/states/states.asp
Vaccine catch-up schedule	http://www.cdc.gov/nip/publications/pink/AccSch00.pdf
Vaccine information statements	http://www.cdc.gov/nip/publications/VIS
The Vaccine Page	http://www.vaccines.com
Vaccine price list	http://www.cdc.gov/nip/vfc/cdc_vaccine_price_list.htm
VFC	http://www.cdc.gov/nip/vfc/

Key: AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; MMWR, Morbidity and Mortality Weekly Report; VFC, Vaccines For Children.

monplace for a pharmacist. As a facilitator, pharmacists continue to educate and motivate the public about immunizations; however, they assume a more active role by ensuring that individuals actually receive their immunizations. This has been accomplished by the development of immunization programs that are offered in community pharmacies. As early as 1982, ambulatory care pharmacists in Georgia instituted a program to identify and immunize patients at risk for pneumonia and influenza.[17] In 1985, community pharmacies in Denver, Colorado, began to invite nurses to administer vaccines to the public. The early 1990s witnessed the development of similar programs in numerous chain pharmacies.[18] As facilitators, pharmacists have also played an active role in referring individuals in need of immunization to the county health clinic, a local physician, or nurse practitioner. Even though all pharmacies do not offer immunizations, the referral of patients continues to be an active area of immunization advocacy.

In 1994, the University of Washington School of Pharmacy and the Washington State Pharmacists Association developed the first coordinated program to train pharmacists to administer immunizations.[19] With this development, the need to host others, (e.g., nurses) in the pharmacy to provide immunizations began to decrease in states that allowed pharmacists to administer drugs. As of June 2001, 32 states explicitly authorize pharmacists to vaccinate.[20] Although the role of facilitator is important in connecting those in need of immunizations to those who can provide the vaccine, there are opportunities for pharmacists to expand their level of advocacy by becoming an immunizer.

For pharmacists to achieve the highest level of immunization advocacy, a number of responsibilities and decisions must be finalized. These responsibilities have been broken into the following categories: legal/regulatory, training, practice requirements, compensation, and documentation.

Legal/Regulatory

If a pharmacist is interested in developing an immunization program, the principle legal issue that must be addressed is how that state views the administration of drugs by a pharmacist. As mentioned previously, more than 30 states currently authorize pharmacists to vaccinate. If you are not sure, check with your state board of pharmacy to determine your options. If your state currently does not allow pharmacists to administer drugs, this would be an opportune time to get involved with your state pharmacy association and state board to attempt to change your state pharmacy regulations. If your state allows pharmacists to administer medications, additional legal and regulatory issues should be addressed. Depending on a state's practice regulations, initiating a patient care service, such as an immunization program, requires a pharmacist to establish a collaborative practice agreement or protocol with a prescriber. As an immunizer, a

pharmacist is at risk of needle sticks and exposure to blood-borne pathogens. Employers and employees must become familiar with the regulations of the Occupational Safety and Health Administration to minimize potential harm to all employees.[21]

Training

As mentioned previously, certificate programs represent the primary method used to educate and train interested pharmacists in how to develop a pharmacy-based immunization program. The training programs available provide individuals with the knowledge, tools, and encouragement to achieve the highest level of advocacy. A list of the organizations offering such programs is provided in Table 3. The training programs are offered at various times of the year and in various locations. Contact the listed organizations or your state pharmacy association to identify a program near you.

Although many of the training programs focus on practicing pharmacists, pharmacy students have also become active in advocating immunizations. Students in all 81 APhA Academy of Students of Pharmacy chapters and 40 Student National Pharmaceutical Association chapters have been involved with *Operation Immunization: The Nation's Pharmacy Students and Practitioners Protecting the Public Health*. Since its inception in 1997, *Operation Immunization* has helped provide more than 125,000 vaccinations.[22]

Practice Requirements

Although there are levels of advocacy, there are also levels of program development. The range of possible levels could start in an apothecary-style pharmacy with a single pharmacist providing immunizations to individuals in between filling all the prescriptions to a large pharmacy practice (independent or chain store) where the immunizations are provided to patients in a separate, private room with pharmacists and support personnel dedicated entirely to this service.

Table 3 Organizations providing standardized training in pharmacy-based immunizations

Organization	Internet address
American Pharmaceutical Association	www.aphanet.org
Centers for Disease Control and Prevention	www.cdc.gov
National Community Pharmacists Association	www.ncpanet.org
Washington State Pharmacists Association	www.PharmCare.org

In the *2000 NCPA-Pharmacia Digest*, responding independent pharmacists reported that on average, 21% of all respondents offered immunizations. Based on the pharmacy's sales volume, the range of offerings was 9% for $500,000 to $750,000 per year in sales to 42% in pharmacies with more than $4,000,000 per year in sales.[23] Generally, vaccine program offerings increased as sales volume increased. Similarly, the percentage of pharmacies offering an immunization service tended to increase as square footage increased. Based on the pharmacy's total square footage, the range of offerings was 11% for pharmacies with less than 1000 square feet to 32% in pharmacies larger than 4000 square feet.[24]

There are numerous examples of immunization programs being offered in independent pharmacies, as well as in chain pharmacies. Although there are a number of differences among these practice sites—including, but not limited to, staff size, physical space, and facility location—in all cases, the development of an immunization program is possible. Staff size is a critical issue for a pharmacy developing an immunization service. Some questions that should be asked are "Who will be the immunizers?", "How will this service effect work flow?", and "Will staff be dedicated to the immunization program, or will immunizations be administered by staff in between regular scheduled duties?" In regards to physical space needs, the minimum requirements for providing immunizations should include space with privacy for administering injections (with room to sit and possibly to lay down in case of an emergency), a dose-preparation area, and a place for patients to wait after the immunization.[25,26] The physical space used for immunization programs has varied from a chair at the end of the counter separated from the waiting area by a partition or curtain, to stock rooms converted into administration areas, to using the owner's/manager's office on scheduled days, to having separate counseling facilities already available. When asked, most immunizers shared that the service was easier to set up than expected and most facilities host such a service. Also, future immunizers will obtain a large amount of information regarding staff and physical needs through the respective training programs offered. Another requirement for this service is a refrigerator with freezer for storage of the vaccine supplies. Vaccine products have specific storage requirements, with standard temperature ranges, so the presence of a quality refrigerator/freezer is critical to the service. A back-up

plan, such as a cooler or alternative power source for the refrigerator, is also important in case of power interruptions of greater than 24 hours.[27]

Compensation

The critical aspect of any service is the covering of costs incurred to provide the service and profit to sustain not only the service, but also the business as a whole. For immunization programs, as with any patient care service developed in a pharmacy, there will be direct and indirect costs associated with the service. Direct costs are those that would not be incurred by the business if the service were not performed, and indirect costs are those incurred even if the service in question was not developed.[28] Although each pharmacy is unique, with its own needs and requirements, the following examples are areas to consider in determining potential costs of such a program. As for direct costs, areas such as service personnel costs, specialty training, additional liability protection, supplies and equipment, service workspace, service-specific advertising and promotion, and additional information resources must be analyzed to help determine the overall costs of this service. To calculate overall costs, indirect costs must also be added to the formula, such as personnel costs of nonservice personnel, rent, utilities, taxes, insurance, general advertising and promotion, and general repair and maintenance. Pricing of each immunization will depend on a number of variables. By having the expected costs of the service, coupled with the cost of the product and the other factors such as competition, demand, standard rates, and image, a price for each immunization may be determined.

For an immunization service, there are a number of methods for compensation. The first method is patients paying cash for the immunization. Patients are familiar with this payment method based on the model of county/state health clinics that have long charged a fee for immunization administration. The second method relates to billing a patient's third-party payer. In some cases, vaccines are paid for as a prescription would be, sent electronically, and the pharmacy is reimbursed for the vaccine as well as an administration fee. The inclusion of an administration fee varies with groups, so an administration fee may also be collected from the patient.[29] In other cases, patients pay cash for the immunization and receive a detailed receipt, listing the type of vaccine, appropriate billing code, and amount paid. The patients are then responsible for submitting the claim to their own insurance company for reimbursement. The third method is billing medicare. To claim reimbursement under medicare, the pharmacist, pharmacy, or both must apply for a medicare provider identification number as an immunizer from the local medicare part B carrier.

Both pharmacists and pharmacies use Health Care Finance Administration (HCFA) Form 855, Provider/Supplier Enrollment Application, to request a provider number. This form may be obtained from medicare part B carriers or provided by the previously mentioned training programs. This is a cursory review of medicare policies. Training programs will provide additional details, or contact your local medicare part B carrier, HCFA regional office, or other pharmacy reimbursement publications.[30] A fourth method of compensation is direct contracts with local area employers. By contracting with an area employer, pharmacists have administered influenza and pneumococcal vaccines to all employees. This type of on-site program can be offered to various businesses, such as plants, office-based facilities, and health care-related facilities, such as assisted living facilities and adult family homes.[31] One popular place for a traveling immunization program has been schools. This type of service primarily focuses on the adults (teachers, staff members); however, some pharmacies have also established child immunization programs. The final method involves special programs that provide funding to specific populations. One such program is VFC. Begun in 1994, children eligible for medicaid, uninsured, Native American, or Alaska Natives may receive vaccinations. Vaccine providers are supplied the vaccines for free. Although some immunization programs charge a small administration fee, all eligible children will receive an immunization, regardless of whether a fee can be paid. Additional details for the VFC program are available by contacting your state immunization coordinator or state department of health.

Documentation

Documentation of vaccination is critical to an immunization service. In many cases, reimbursement is not obtained without proper documentation. However, with a large portion of immunizations paid for in cash and the need to know which patient received which vaccination in case of a recall, there are some documentation issues that must be addressed. The use of software, either specifically designed for vaccines or general patient management, is available from several sources. Free software is available from the Center for Disease Control and Prevention's (CDC's) National Immunization Program (www.cdc.gov).[32] If patient profile software is used to track immunizations, it is critical for an easily accessible, permanent record to be established for im-

munizations because prescription records can be purged and even deleted over time, based on state board regulations. Depending on the requirements of individual states, immunizers must determine if there is a requirement for the use and filing of consent forms, protocol agreements, and other related documentation. The various training programs provide necessary information regarding documentation requirements, or your respective state board of pharmacy can be contacted directly with specific questions.

RESOURCES FOR VACCINE INFORMATION

A variety of resources are available for pharmacists interested in beginning a pharmacy-based immunization practice. Some of the best resource people include state health officers; county health clinic physicians; state department of health vaccine coordinators, especially those that administer the CHIP or KidCare-like immunization programs; and local, board-certified primary care and infectious disease physicians. There are also a number of excellent web sites (see Table 2). The primary and most reliable source for vaccine and immunization information is the CDC web site. Most reliable information about vaccines and immunization on other web pages is based on information first published in the public domain by the CDC in their journal, *Morbidity and Mortality Weekly Report* (MMWR). For those interested in keeping tabs on up-to-the-minute vaccine and immunization changes and recommendations, one should access the CDC listserv. This service forwards all issues of MMWR to your e-mail in portable document format (pdf) for viewing on freeware—Adobe Acrobat Reader.

Table 4 Immunization networks, organizations and listservs

Resource	Web address
Allied Vaccine Group	http://vaccine.org
APhA	http://www.aphanet.org (Pharmaceutical Care)
APhA-Pharmacist Immunizer Listserv	apha-immpharm-subscribe@egroups.com
Immunization action coalition	http://www.immunize.org
MMWR subscription	listserv@listserv.cdc.gov
National immunization program	http://www.cdc.gov/nip
NNII	http://www.immunizationinfo.org
VISI	http://www.cdc.gov/nip/visi

APhA, American Pharmaceutical Association; MMWR, Morbidity and Mortality Weekly Report; VISI, The Vaccine Identification Standards Initiative; NNII, National Network for Immunization Information.

NETWORKS AND ORGANIZATIONS

There are a number of immunization and vaccine networks designed to help inform professionals and the public about immunization efforts regionally and nationally. Listservs can also be helpful to those having specific questions in need of expert commentary. One should be cautious, as there is as much helpful information about immunizations and vaccines as there is unsubstantiated and erroneous information. Look carefully at who sponsors and writes the information that you are reading. If the information seems inflammatory or extremist, it is probably not scientifically valid or presents a skewed interpretation of the facts. Also, whenever reading tertiary literature, pull the references and interpret the information yourself if you are in doubt of its validity. This is the best method of ensuring that you are making decisions based on first-hand information. Of course, the referenced material must come from a refereed, reputable source or else it too is suspect. Table 4 lists some reliable networks, organizations, and listservs that pharmacists can access to augment their knowledge base.

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Pharmacist Prescribing

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INTRODUCTION

The modern practice of pharmacy is in a state of evolution. One important element of that evolutionary state is the inclusion within the scope of practice of some pharmacists in some jurisdictions of the right to prescribe medications to a patient. A pharmacist who undertakes the new skill of prescribing must acquire the appropriate skills consistent with the sophistication of the task or risk liability on various levels. This article will summarize critical legal and ethical issues associated with the evolving function of the pharmacist prescriber.

THE EVOLVING ROLE OF THE PHARMACIST AND EXPANSION OF SCOPE OF PRACTICE

Scope of practice is defined as those duties and limitation of duties placed on pharmacists by applicable laws. Traditionally, the scope of practice of a pharmacist was limited to accurately filling and dispensing valid prescriptions as directed by the treating physician.[1,2] This was a largely nonjudgmental role. However, in the past 20 years, the role of pharmacists has evolved from technical to more judgmental, broadening their scope of practice.[3] Generic substitution[4] and therapeutic substitution, usually through a formulary system,[5] represented initial expansive tasks undertaken by pharmacists. The Omnibus Budget Reconciliation Act of 1990 (P.L. 101-508) (OBRA 90)[6] further expanded the responsibility of the pharmacist to include counseling and drug utilization review.

Clinical pharmacy[7] evolved into pharmaceutical care, which included therapeutic outcome monitoring and disease-state management to improve quality of life and minimize long-term health costs.[8] Pharmacists are now receiving compensation from third-party payers for such cognitive services and have expanded their clinical skills.[9–11] There is a move by more and more states to seek prescriptive authority for pharmacists, enabling seamless and effective monitoring and treatment of patients, especially those with chronic diseases on maintenance therapy.[12]

PRESCRIPTIVE AUTHORITY

Dependent Versus Independent Prescribing Authority

Physicians exercise plenary independent prescribing authority. Plenary authority refers to the ability to prescribe all drugs, treatments, and devices, including controlled substances, without supervision, control, or oversight by another profession.[13] Independent prescribing authority means that the prescriber has the sole authority to make treatment decisions and is wholly responsible for the resultant outcomes.[14]

Limited independent prescribing authority permits independent prescribing within the bounds of the prescriber's scope of practice or within the restrictions of a certain formulary of drugs. Doctors of dental surgery, doctors of veterinary medicine, and doctors of podiatric medicine have limited independent prescribing authority in every state; this authority is limited to their scope or course of practice.[15]

Prescribers with dependent prescribing authority are dependent on a prescriber with independent authority for their own authority, and the discretion involved in this authority may be limited by written guidelines, a protocol, or supervisory approval. Pharmacists with dependent prescribing authority have prescribing authority delegated by a physician on the basis of that physician's belief that the pharmacist has the professional judgment and skills necessary to perform the delegated duties. The pharmacist shares with the collaborating physician the risks and responsibility for the patient's overall outcome.[16]

In Collaborative Drug Therapy Management (CDTM), the pharmacist and physician work in collaboration to manage a patient's drug therapy. Through the use of written guidelines or protocols, the pharmacist may be delegated authority to collect and review patient drug histories, initiate and/or modify drug therapy, order and evaluate laboratory tests relating to drug therapy, and order and/or perform drug-related patient assessments. The written protocol is usually specific to a certain pharmacist and a certain physician and may also define the

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006331

individual and shared responsibilities of the physician and pharmacist. CDTM protocols authorizing pharmacists to initiate or modify drug therapy in effect give the pharmacist dependent prescribing authority.[17]

State Perspective

States have the "police power" to take regulatory actions to protect the public health, welfare, and safety of their citizens.[18] Thus, states have the authority to license health care professionals and to dictate which health care professionals can prescribe medications. State statutes called Pharmacy Practice Acts dictate what duties pharmacists may perform.

Many states have enacted legislation that expands the practice of pharmacy to include CDTM. As of June 2000, there were at least 27 states granting the statutory authority for the practice of CDTM.[19] The nature of CDTM prescriptive authority for pharmacists varies from jurisdiction to jurisdiction and its definition is in flux. In some jurisdictions, the pharmacist will be required to acquire advanced training and experience in order to participate in such a role. In other jurisdictions, delegated prescriptive authority may be restricted to certain settings, such as health care institutions or nursing homes.

At least one author has defined pharmacist prescriptive authority as "the practice of pharmacy whereby a pharmacist has jointly agreed, on a voluntary basis, to work in conjunction with one or more practitioners under protocol whereby the pharmacist may perform certain functions authorized by the practitioner or practitioners under certain specified conditions or limitations."[20] This approach does not contemplate prescriptive authority as currently practiced by physicians. Another article in this volume will expand on CDTM.

Regarding independent prescriptive authority, no pharmacists in any state have plenary independent prescriptive authority. Florida is the only state where pharmacists enjoy true independent prescriptive authority; however, this authority extends only to a limited formulary of drugs, listed in 21 categories. There are other restrictions as well. For example, a pharmacist cannot prescribe any injectable drugs nor any oral drugs for a pregnant woman or nursing mother. The pharmacist cannot exceed the manufacturer's recommended dosage or in any case give more than a 34-day supply.[21]

Federal Perspective

The sale and distribution of drugs in the United States is primarily controlled by two legislative acts. They are the Federal Food, Drug and Cosmetic Act (FDCA)[22] and the Federal Controlled Substances Act (CSA).[23] The FDCA involves the establishment of rules and regulations by which drugs are imported, manufactured, distributed, and sold in the United States, and the CSA involves the prevention and control of the abuse of controlled substances. Federal law does not dictate "who" may prescribe and does not state provisions for licensure.[24,25] The CSA also fails to establish specific criteria regarding who may prescribe, merely stating that the prescriber must be licensed to prescribe under state law and be registered with the Drug Enforcement Administration (DEA) to prescribe controlled substances.[26] The supremacy clause (U.S. Constitution, Article VI, Paragraph 2) establishes supremacy of federal law over state law; federal agencies enjoy freedom from state or local regulation where Congress has not affirmatively made federal agencies subject to state law.

Within federal services and agencies, such as the Armed Services, Indian Health Service (IHS), and the Veterans Administration (VA), there may exist directives or regulations that confer the authority to prescribe on certain classes of practitioners. Federal facilities require that their health care professionals be licensed by at least one state, but the scope of practice of these professionals may be broadened or limited by written policies.[27]

The federal government has experimented with various models of pharmacist prescribing.[28–32] The VA and the IHS appear to have the most liberal policies toward pharmacist prescribing.[33,34] In the VA, clinical pharmacy specialists are required to have an advanced degree or have completed an accredited residency (e.g., an American Society of Health Systems Pharmacy, ASHP, accredited residency) or specialty board certification (e.g., a Board of Pharmaceutical Specialties, BPS, certification) before they may prescribe medications within their scope of practice. The scope of practice is established within the local VA facility. Once this criterion is satisfied, the clinical pharmacy specialist may function as an independent health care provider. In the IHS, pharmacists can be credentialed to provide primary care and use their prescriptive authority to evaluate and manage the care of certain patients.[35]

LIABILITY AND ETHICAL CONSIDERATIONS

Traditionally, the learned intermediary doctrine, shielded drug manufacturers and pharmacists from liability by imposing on the physician the duty to explain and to warn the patient about the effects of specific medications. Courts have remained reluctant to impose a "duty to warn" on pharmacists dispensing prescriptions, unless

pharmacists voluntarily undertake such a duty, e.g., by advertising that they will undertake this duty.[36,37] However, mandated requirements for patient counseling will likely soon impact court decisions. As the scope of practice expands and judgmental functions increase, so does the potential for liability.

As pharmacists gain prescriptive authority, as well as responsibility for primary management of certain medical conditions, they must acquire new skills and a new awareness of the associated legal and ethical pitfalls. Pharmacists will be held accountable for negligence in performing new tasks or for practicing outside the scope of their practice. Pharmacists must also be aware of potential conflicts of interest, particularly in the managed care setting. Areas that have historically been problems for physicians may also become problem areas for pharmacists.[38–40]

Civil Actions

A patient alleging harm by a prescribing pharmacist can allege that the pharmacist, acting within the scope of practice of the profession of pharmacy, has performed in a fashion that is substandard and that, as a direct result of that substandard performance, the patient has suffered harm. This patient would allege that the pharmacist was negligent. A plaintiff can establish negligence by establishing that a duty to conform to a certain standard of conduct existed, that the duty was breached, that damages occurred, and that there was a reasonably close causal connection between the conduct and the resulting injury or damage.[41]

Traditionally, malpractice actions against pharmacists have stemmed from dispensing errors.[42] Dispensing errors can be distinguished from prescribing errors. Under a dispensing error standard, if a pharmacists fills a prescription in the manner in which it was ordered by the prescriber and there are no other obvious contraindications to the prescription, the pharmacist is not liable for any harm that comes to the patient. In short, courts have viewed dispensing as a nonjudgmental technical task that should be undertaken with great care and accuracy. Even alleged errors associated with faulty therapeutic interchanges (e.g., incorrect dosage adjustments made when one drug is dispensed in place of another) are dispensing errors, because pharmacists follow a protocol, decided on institutionally, when substituting one drug for another. Hence, the liability applies to the institution, which exercised the judgment, rather than to the pharmacist, who executed the decision. There is substantial case law on systems errors, based on the theory of respondeat superior, a doctrine in which the employer accepts responsibility for the tort liability of the employee, and corporate or institutional negligence, where protocols and procedures were inadequate to prevent errors.[43]

Pharmacists assuming additional clinical duties are at increased risk for malpractice lawsuits because patient assessment, treatment, and prescribing are more complex functions than making sure a prescription is filled correctly or counseling patients about adverse reactions. There is potential for negligence in any aspect of patient care, including taking a history, performing a physical examination, interpreting a laboratory test, or prescribing or renewing a drug.

Administrative Actions

The voluntary assumption of different or more sophisticated clinical duties by pharmacists can involve administrative action.[44,45] Administrative actions are brought by the state board and involve the statutorily authorized revocation or suspension of a license upon administrative finding of unprofessional conduct. Examples of unprofessional conduct for physicians are prescribing a drug without medical justification, prescribing a drug in excessive amounts, and unlawfully dispensing a controlled drug to a known addict. Unprofessional conduct might also include ethical violations like supplying a patient with drugs in return for sex and performing inappropriate physical examinations for sexual purposes.

State boards of pharmacy will have to develop guidelines and procedures to address the expanded clinical functions of pharmacists so that adequate oversight can be maintained. While tightly drawn CDTM agreements and protocols can eliminate some problems, they cannot eliminate all the problems.

Criminal Actions

Criminal sanctions may be imposed on health care professionals in certain situations.[46,47] These situations include improper prescribing of controlled substances, Medicaid and Medicare fraud, sexual abuse of patients, and even negligent care of patients.

Prescribers must be careful in prescribing controlled substances; it has been held that a licensed physician who prescribes controlled substances outside the bounds of professional medical practice is no different from a drug "pusher" subject to prosecution under the Controlled Substances Act. (21 U.S.C.S.§841[a][1]). Criminal liability may extend to the prescribing of controlled substances.[48]

The position of the Drug Enforcement Administration (DEA) is that if a state recognizes the authority of a pharmacist to prescribe controlled substances, then the DEA will register pharmacists as midlevel practitioners. Spe-

cifically, in 21 CFR §1304.02(f), the DEA establishes a new category of registration, midlevel practitioners, under which advanced-practice nurses, physician assistants, and others (e.g., pharmacists) will receive individual DEA registration granting controlled substance privileges consistent with authority granted them under state law. Other DEA regulations, 21 CFR §1301.24(b) and 1301.24(c), exempt agents and employees of a registered individual practitioner, hospital, or institution from the requirement of individual registration when they administer, dispense, or prescribe controlled substances in the course of their official duties or business. Thus, individual registration may not be necessary in order for pharmacists to prescribe controlled substances in an organizational setting.

It has long been clear that pharmacists would be liable for exchanging controlled drugs for sexual favors from either patients or nonpatients. A pharmacist may now also be liable for writing a prescription in exchange for sexual favors. Furthermore, pharmacists doing physical examinations must avoid behaviors that could be construed as inappropriate touching or sexual assault, both of which could result in criminal or administrative sanctions.

Smith[49] stated that there is currently an "enthusiasm for professional accountability, especially when human life is lost." Criminal prosecution of negligence involving deliberate disregard of patient safety effectively serves the dual purpose of deterrence and punishment.[50] Like physicians, pharmacists will have to be sensitive to this added potential liability as they undertake the clinical care of patients, including prescribing medications.

Standard of Care

In analyzing whether a duty has been breached in a medical malpractice civil action, an administrative action, or a criminal case, the court considers whether the health care professional met the standard of care. If a lawsuit were brought because of damages caused by an incorrectly filled prescription, the court would look at the care that a reasonably prudent pharmacist in the community would have provided in the same or similar circumstances. Because prescribing drugs has traditionally been a physician function, a pharmacist undertaking this function may be held to the standard of care of a physician rather than the traditional standard of care of a pharmacist. This may be a more stringent standard because most physicians have more clinical training and experience than most pharmacists. If pharmacists hold themselves out as competent to physically assess patients and prescribe medications, citing additional degrees and board certification, the court may decide to hold them to the higher standard.

Managing Risk: Boundaries, Conflicts of Interest, Attitudes, and Skills

To minimize the risk of liability, pharmacists must know their scope of practice and not exceed it. Phillips[51] stated that an adequate legal definition of the scope of practice of a health care professional, as well as realistic standards for that profession, is necessary in order for the courts to correctly apportion liability for wrongful conduct and correctly apply malpractice theory.

CDTM or prescribing protocols must be written carefully, and they should be reexamined and updated regularly to ensure that they are not based on a standard too high to be reasonably met at all times and in all settings. In the pharmacist's judgment, a patient's condition or treatment requirements may seem only slightly inconsistent with the written protocol; however, pharmacists must be aware that protocols may leave little room for discretion. Pharmacists must be careful not to overstep the boundaries of their scope of practice, for this could result in a charge of practicing medicine without a license.

Another issue to be considered is the inadvertent misrepresentation of one's profession to patients. If a pharmacist performs a medical procedure or writes a prescription for a patient while the patient is mistaken about the professional status of the pharmacist, the pharmacist could potentially be charged with breach of the duty to obtain informed consent.[52]

The pharmacist who obtains patient histories, conducts physical examinations, orders laboratory tests, and prescribes medications must adopt new attitudes and develop new judgment skills. Communication is paramount, both with patients and with other health care professionals, particularly physicians. It has been said that poor communication and emotional issues are at the heart of nearly all medical malpractice actions.[53] Interdisciplinary communication is vital to ease the passage of pharmacists into expanded prescribing roles; good communication will enhance collaboration in patient care and diminish perceived threats to physicians' autonomy and authority. Obviously, expanded clinical roles for pharmacists will require increased patient contact and strong communication skills. If the patient and the pharmacist fail to understand each other, the pharmacist's risk of liability is increased.

POLICY ISSUES

The expansion of pharmacist prescribing may be affected by marketplace factors such as the abundant availability of other nonphysician prescribers,[54] the current focus of

the health policy arena on medication errors,[55] and the nationwide shortage of pharmacists.[56] CDTM is a politically acceptable stepping stone to independent prescriptive authority and is supported by many leading national pharmacy organizations.[57] On the other hand, the American Medical Association has taken a strong stand against nonphysician prescribing, and it will take time for pharmacists to establish themselves as prescribers.[58] Traditionally, pharmacists have been gatekeepers and patient advocates. However, if suddenly the pharmacist becomes a physician surrogate, the pharmacist's role will be seen differently by the patient. The pharmacist will be acting in a more cognitive discretionary manner and asking for more compensation; from the patient's perspective, the pharmacist will also become less available or approachable. Given the complexity of medications and the volume of medication errors, there will be an interest by the public in retaining pharmacists in their traditional roles as gatekeepers unless these matters can be addressed effectively.

CONCLUSION

This article has summarized critical legal and ethical issues associated with the evolving function of the pharmacist prescriber. The purpose of this chapter is not to discourage pharmacists interested in prescribing, but to review critical issues associated with a new role. With proper training, communication with the patient and the patient's physician, adherence to the appropriate standard of care, avoidance of ethical and criminal breaches, the modern pharmacist will be able to contribute even more to the health care team.

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PROFESSIONAL RESOURCES

Pharmacotherapy, The Journal of Human Pharmacology and Drug Therapy

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INTRODUCTION

Pharmacotherapy, The Journal of Human Pharmacology and Drug Therapy, is the official journal of the American College of Clinical Pharmacy (ACCP) and is published monthly. *Pharmacotherapy* is peer reviewed and is indexed in *Index Medicus*, *Current Contents*, *Exerpta Medica*, *Biological Abstracts*, *Chemical Abstracts*, *Current Awareness in Biological Sciences*, and *Referativnyi Zhurnal*.

Pharmacotherapy seeks out and publishes original, clinically relevant research, evidence-based reviews about drugs and therapeutics, and pharmacoeconomic and population-based therapeutic outcomes studies. Instructive case reports are also published. Editorial departments within the journal include Original Research Articles, Brief Reports, Reviews of Therapeutics, Mini-Reviews, Practice Insights, and Case Reports. The American College of Clinical Pharmacy publishes all of its official papers (e.g., official position statements, white papers) as well as its meeting abstracts in *Pharmacotherapy*. With some regularity, *Pharmacotherapy* publishes peer-reviewed supplements.

AVAILABILITY OF *PHARMACOTHERAPY* ARTICLES, ABSTRACTS, AND INSTRUCTIONS FOR AUTHORS ONLINE

Pharmacotherapy (1999 and later issues) is available online in a searchable, full-text, full-graphics format, (downloadable HTML files) free of charge through Medscape.com. You must sign up once for Medscape's free service. Thereafter, you need only to use a password to gain access to this valuable online library and information source. To navigate directly to the "*Pharmacotherapy* reading room" on Medscape, the direct URL is http://www.medscape.com/viewpublication/132_index. Alternatively, you may go to medscape.com and utilize the many resources available on this site while navigating to the "*Pharmacotherapy* reading room."

Abstracts of all *Pharmacotherapy* articles (from 1997 onward) as well as a downloadable/printable version of *Pharmacotherapy's* "Instructions for Authors" are posted in the *Pharmacotherapy* section of the ACCP Web site (www.accp.com).

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EDITORIAL BOARD AND SCIENTIFIC EDITORS

The Editor-in-Chief enjoys the counsel and support of a multidisciplinary Editorial Board of over 40 respected clinicians, researchers, and other scientists. In addition, a small, elite core of Scientific Editors, composed of nationally and internationally recognized scientists and thought leaders, help set editorial policy, help determine the journal's direction, and actively participate as Field

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006276

Editors, inviting important papers and directing the pivotal elements of their editorial life.

A BRIEF HISTORY OF *PHARMACOTHERAPY*

Pharmacotherapy, The Journal of Human Pharmacology and Drug Therapy, was founded in 1981 by Russell R. Miller, Pharm.D., Ph.D., a young, fiery visionary who conceptualized a journal whose embrace would include all scientifically anchored aspects of clinical pharmacy and clinical pharmacology. For several years previously, Dr. Miller had been a Column Editor for the *American Journal of Hospital Pharmacy*, captaining a column prophetically named by him, "Pharmacotherapy." Armed with this experience, his vision, and his famous energy and laser focus, Dr. Miller developed and brought *Pharmacotherapy* to market nearly single-handedly. Early on, the value of the journal was recognized by William A. Gouveia, Director of Pharmacy at Tufts-New England Medical Center in Boston, who instrumentally and graciously supported the journal and has provided hospital space for the journal to nurture and grow.

The journal grew steadily under Dr. Miller's steady hand and in 1985, he appointed Richard T. Scheife, Pharm.D., FCCP, as Deputy Editor of *Pharmacotherapy*. Since 1986, following the untimely death of Russell Miller, Richard Scheife has served as Editor-in-Chief.

Because of their shared commitment to improving the science and practice of pharmacotherapy, and because of their common long-term goals regarding the professional and scientific direction of the journal, *Pharmacotherapy* and ACCP initiated an affiliation agreement in 1988 whereby *Pharmacotherapy* became the official journal of the American College of Clinical Pharmacy. This relationship continued to strengthen and, in 1994, *Pharmacotherapy* became part of the ACCP family. Today, *Pharmacotherapy* continues to flourish and has become one of the preeminent scientific journals in the area of pharmacy and clinical pharmacology.

FUTURE DIRECTIONS

The future directions for *Pharmacotherapy* can be summed up in the preamble of our vision statement: "*Pharmacotherapy* will become the preeminent journal in the broad field of pharmacotherapy and clinical pharmacology by serving as a knowledge source and publication venue for all health disciplines committed to optimizing drug therapy outcomes." Further, *Pharmacotherapy* will be the source of first choice by faculty when teaching health professionals about drugs and therapeutics. *Pharmacotherapy* will fully utilize all relevant forms of media to allow the broadest accessibility to *Pharmacotherapy's* important and high-impact knowledge.

Pharmacotherapy Self-Assessment Program (ACCP)

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INTRODUCTION

The *Pharmacotherapy Self-Assessment Program* (PSAP), published by the American College of Clinical Pharmacy, is a series of books that provides information on the therapeutic use of drugs. A broad range of therapeutic topics is covered. The topics included in PSAP are presented in a modular, curricular format (Table 1). Books, each containing two to three modules, are distributed every three months throughout the life of each edition.

DESCRIPTION

The focus of PSAP is on gathering data to make informed decisions and to support complex therapeutic decision making and problem solving. Information is presented and summarized through the use of tables, diagrams, figures, and algorithms to assist in decision making. Each chapter includes an update of pharmacotherapy with a focus on the provision of pharmaceutical care to improve patient outcomes, annotated references that direct health care professionals to additional resources for further study, and multiple-choice self-assessment questions in a case study format. A detailed rationale for the answers is provided, with references, to enhance the learning experience. The detailed rationale explains the approach that the author would take in evaluating and treating the patient described in the case. The program is designed to provide an update of the drug therapy of diseases with information from the three years previous to publication. PSAP emphasizes an extremely short time frame between when the text is written until it is printed and distributed. This resource provides a professional development tool that permits pharmacists to work at an individual pace.

Table 1 Topics by edition

First Edition	Second Edition	Third Edition	Fourth Edition
Cardiovascular	Cardiovascular	Cardiovascular	Cardiovascular
Infectious diseases	Critical care	Critical care	Systems of care
Neurology	Infectious diseases	Infectious diseases	Sites of care
Psychiatry	Biostatistics	Neurology	Respiratory
Respiratory	Research design and	Psychiatry	Endocrinology
Gastroenterology	literature evaluation	Research, biostatistics, and	Rheumatology
Nephrology	Drug information	drug information applications	Infectious diseases
Endocrinology	Technologies and strategies	Consensus-driven	The science and practice
Immunology	Drug regulatory process	pharmacotherapy	of pharmacotherapy
Oncology	Respiratory	Respiratory	Critical care
Nutrition	Nephrology	Endocrinology	Urgent care
Fluid and electrolytes	Gastroenterology	Nephrology	Neurology
	Endocrinology	Immunology	Psychiatry
	Immunology	Gastroenterology	Gastroenterology
	Nutrition	Nutrition	Pediatrics
	Oncology	Pediatrics	Nephrology
		Oncology	Hematology
		Women's health	Oncology
			Women's health
			Men's health

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006390

HISTORY OF PSAP

PSAP was initiated in 1991 with the goal of developing and distributing a high-quality, intensive, structured program for advanced-level clinical practitioners. Other objectives of the program included: 1) assisting other structured programs (e.g., staff development or residencies) in upgrading the clinical competence of clinical pharmacy generalists; 2) assisting advanced-level clinical practitioners in maintaining clinical competence; 3) emphasizing decision-making skills for complex clinical problems.

The goals and objectives of this program have been carried out consistently through the dedication and direction of the editorial boards (Table 2), the quality writing of leaders in the field of pharmacotherapeutics, and the input of skilled reviewers. Since the second edition of PSAP, the Board of Pharmaceutical Specialties acknowledges its quality by recognizing participation in PSAP as a method of obtaining recertification as a Board Certified Pharmacotherapy Specialist.

CONTINUING FOCUS OF PSAP

PSAP is continuing to focus on innovations in the drug treatment of diseases. Additional emphasis is being placed on the integration of alternative medicine into the treatment plan and the role of genomics in the prevention and treatment of diseases. Information is being provided on new ways that patients may choose to access the health care system, including home health care and telemedicine. In addition, new sources of drug information are discussed and described.

Consistent with the progressive nature of the PSAP series, innovative formats for delivery of PSAP information are being evaluated. These will include a version available on the Internet, starting with the fourth edition. The online version of PSAP provides the same information as the print version but with additional functionality, including the ability to take the exams online. The online version also permits access by pharmacists in remote areas of the world.

Table 2 Editorial boards by edition

First Edition	Second Edition	Third Edition	Fourth Edition
Barry L. Carter, Pharm.D., FCCP (Chair)	Barry L. Carter, Pharm.D., FCCP (Chair)	Barry L. Carter, Pharm.D., FCCP, BCPS (Chair)	Bruce A. Mueller, Pharm.D., FCCP, BCPS (Chair)
David M. Angaran, MS, FCCP	David M. Angaran, MS, FCCP	Kathleen D. Lake, Pharm.D., FCCP, BCPS	Karen E. Bertch, Pharm.D.
Thomas Sisca, Pharm.D., FCCP	Kathleen D. Lake, Pharm.D., BCPS	Marsha A. Raebel, Pharm.D., FCCP, BCPS	Teresa S. Dunsworth, Pharm.D., BCPS
	Marsha A. Raebel, Pharm.D., FCCP, BCPS	Karen E. Bertch, Pharm.D.	Susan C. Fagan, Pharm.D., FCCP, BCPS
		Marc K. Israel, Pharm.D., BCPS, CDE	Mary S. Hayney, Pharm.D., BCPS
		Donna M. Jermain, Pharm.D., BCPP	Mary Beth O'Connell, Pharm.D., FCCP, BCPS
		H. William Kelly, Pharm.D., FCCP, BCPS	Glen T. Schumock, Pharm.D., MBA, BCPS
		Nancy P. Lam, Pharm.D. BCPS	Dennis F. Thompson, Pharm.D., FCCP
		Wendy L. St. Peter, Pharm.D., FCCP, BCPS	James E. Tisdale, Pharm.D., FCCP, BCPS
		Bruce A. Mueller, Pharm.D., FCCP, BCPS	Daniel M. Witt, Pharm.D., BCPS
		Dennis F. Thompson, Pharm.D., FCCP, FASHP	Barbara J. Zarowitz, Pharm.D., FCCP, BCPS

Pharmacotherapy Specialists, Practice Guidelines for (ACCP)

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INTRODUCTION

The purpose of these practice guidelines is to describe the level of clinical pharmacy practice, knowledge, specialized skills, and unique functions that characterize the pharmacotherapy specialist.

Pharmacotherapy is that area of pharmacy practice that ensures the safe, appropriate, and economical use of medications. To function in this capacity requires specialized education and/or structured training in the clinical sciences. The pharmacotherapy specialist possesses unique professional knowledge and skills gained through advanced training in the biomedical, pharmaceutical, and clinical sciences, as well as through practice experiences. The pharmacotherapy specialist is skilled in the use of sound judgment in the collection, interpretation, and application of patient-specific data that are used to assist with the design, implementation, and monitoring of therapeutic regimens. Knowledge and skills of the pharmacotherapy specialist may be acquired through primary academic curricula, postgraduate residency or fellowship training, or innovative and extensive pharmacy practice experiences. The skills of the pharmacotherapy specialist, when applied across the entire continuum of the health care system, benefit individual patients, health care organizations, and society in general. The pharmacotherapy specialist is a licensed pharmacist and graduate of an accredited college or school of pharmacy.

The pharmacotherapy specialist is recognized by the pharmacy, medical, and allied health professions and by society in general as an expert in the area of applied pharmacotherapeutics and as an integral member of the health care team. Regardless of whether the specialist practices in acute or ambulatory care, the pharmacotherapy specialist meets the guidelines outlined in this document by the routine performance of the activities described in the assessment factors as part of daily pharmacy practice responsibilities.

GUIDELINE I

The pharmacotherapy specialist designs, implements, monitors, evaluates, and modifies patient pharmacotherapy to ensure effective, safe, and economical patient care.

Rationale

Using specialized knowledge of pharmacology, pharmacokinetics, pathophysiology, pharmacoeconomics, and therapeutics, the pharmacotherapist takes responsibility for patient outcomes. The pharmacotherapy specialist manages pharmacotherapy by evaluating therapeutic agents in the context of patients and populations and working collaboratively to assure their effective, safe, and economical use. The pharmacotherapy specialist makes clinical observations and incorporates them with information gained from other health care providers to optimize therapeutic decisions. The pharmacotherapy specialist participates in the evaluation of drug efficacy; identifies, reports, prevents, and participates in the management of adverse reactions; and initiates appropriate changes in the pharmacotherapeutic management of patients. This may include the discontinuation of drug treatment regimens, the prevention of unnecessary or potentially harmful treatment regimens, individualized adjustment of therapy in patients having unstable disease entities, management and moni-

This document was approved by the ACCP Board of Regents on January 17, 2000. It replaces "Practice Guidelines for Pharmacotherapy Specialists" (*Pharmacotherapy* 1990, 10:308–311).
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DOI: 10.1081/E-ECP 120006408

toring of chronic drug therapy, or management of the drug formulary.

Assessment factors

1. Collaborates with other health professionals to make therapeutic decisions such as drug and drug product selection, therapeutic drug monitoring, and drug dosing.
2. Participates in the planning and development of patient treatment.
3. Investigates therapeutic alternatives and recommends or initiates the management of patient-related problems based on interpretation of relevant literature and clinical experience. Communicates the results of these investigations to health care practitioners in a manner appropriate to the training, skill, and need of that health professional.
4. Assists in the management, monitoring, and modification of drug therapy in patients with chronic disease.
5. Reviews patient records and orders regarding drug therapy and recommends and initiates changes as appropriate.
6. Evaluates patients by means of interview and, when appropriate, physical assessment to determine past medical history, previous medication use, present medical history, present medication use, present medical condition, and response to therapy. The pharmacotherapy specialist performs accurate and reproducible physical examination in accordance with their formal training and experience.
7. Interprets laboratory and other patient-specific data to aid in determining treatment plans and monitoring response to therapy.
8. Solves therapeutic queries posed by physicians and other health care providers.
9. Identifies complications resulting from drug therapy and recommends or initiates the necessary treatment alternatives to minimize or negate them.
10. Utilizes available state-of-the-art knowledge and technology to assess, improve, and monitor drug therapy regimens.
11. Establishes procedures for detecting significant drug-drug, drug-laboratory, drug-food, and drug-herbal interactions, and develops the necessary means to minimize adverse patient consequences that might result from such interactions.
12. Effectively communicates oral and/or written therapeutic recommendations or other aspects of drug therapy to health professionals, peers, patients, the public, and health care managers.
13. Assesses and participates in the management of patients with drug overdose and patients exposed to poisons.
14. Performs basic cardiac life support, and assesses and participates in drug therapy management during medical emergencies.
15. In conjunction with licensed medical practitioners, develops, manages, and assists in the implementation of pharmacotherapeutic protocols.
16. Works with other health care providers and relevant committees to develop programs for improving drug use and quality of patient care.
17. Documents the economic impact of clinical pharmacy activities for use by organized health care managers, practitioners, institutions, and providers.
18. Identifies therapeutic categories or individual therapeutic agents warranting drug utilization evaluation. Develops and conducts drug utilization evaluation in these targeted areas.
19. Coordinates the timely, accurate delivery of medications to patients in conjunction with other pharmacy practitioners.
20. Utilizes pharmacokinetic principles in the formulation of therapeutic drug regimens.
21. Coordinates the timing and collection of drug concentration samples in biologic fluids, interprets drug concentration results, makes recommendations to physicians regarding dosage adjustments, and monitors response to recommended dosage regimens.
22. Interprets patient-specific data, physical findings, medical history, and other pertinent information to aid in designing treatment plans, and monitors the patient's response to the recommended dosage regimen.
23. Evaluates the biomedical literature to determine optimal therapeutic drug-monitoring strategies and population pharmacokinetic parameters.
24. Interprets and applies population pharmacokinetic data to the design of patient-specific drug dosage regimens.
25. Determines patient-specific pharmacokinetic parameters on the basis of measured drug concentrations and prospectively applies these data to dosage regimen design.
26. Educates health professionals, students, patients, and the public regarding the utility of clinical pharmacokinetics.

GUIDELINE II

The pharmacotherapy specialist retrieves, analyzes, evaluates, and interprets the scientific literature as a means of providing patient- and population-specific drug information to health professionals and patients.

Rationale

Having expertise in literature evaluation and specialized training in therapeutics enables the pharmacotherapy specialist to retrieve and apply drug treatment information. The pharmacotherapy specialist will interpret the primary literature, evaluate its applicability to given patient care situations, and apply it in the synthesis of a solution to patient-specific drug therapy problems.

Assessment factors

1. Identifies and retrieves the best available information about pharmacotherapy by searching appropriate tertiary, secondary, and primary sources. The pharmacotherapist is adept at using computer technology to collect information.
2. Evaluates biomedical and pharmacoeconomic literature to determine criteria for optimal use and monitoring of therapeutic agents.
3. Routinely reviews biomedical and pharmacoeconomic literature relevant to the pharmacotherapeutic management of patient populations.
4. Evaluates the literature with regard to study design and methodology, statistical analysis, and significance of reported data so that appropriate assessments and conclusions may be applied to the solution of drug therapy problems.

GUIDELINE III

The pharmacotherapy specialist participates in the generation of new knowledge relevant to the practice of pharmacotherapy, clinical pharmacy, and medicine.

Rationale

The pharmacotherapy specialist has responsibility for the continuing development and refinement of knowledge regarding the appropriate use of medications. This knowledge may be generated by conducting research and clinical experimentation of therapeutic agents, by devising new and innovative approaches to pharmacotherapy practice, or by evaluating outcomes of new and innovative roles of pharmacotherapy specialists. The pharmacotherapy specialist has the responsibility to effectively convey the results of pharmacotherapeutic research to health professionals, patients, the public, and health care managers.

Assessment factors

1. Identifies pharmacotherapeutic questions to be studied or problems to be solved within the realm of pharmacotherapy practice.
2. Develops, implements, evaluates, and participates in scientifically valid and ethically designed studies.
3. Supports internal and external mechanisms for review of research protocols with regard to study design and protection of human subjects.
4. Collects data regarding the outcomes of patients managed by the pharmacotherapist.
5. Presents research results at scientific meetings and publishes results in the scientific literature.

GUIDELINE IV

The pharmacotherapy specialist educates health care professionals and students, patients, and the public regarding rational drug therapy.

Rationale

Experience and training in education combined with specialized knowledge and skills in pharmacotherapeutics render the pharmacotherapy specialist uniquely qualified to educate health care providers and consumers regarding effective, safe, and economical use of drugs. The specialist may teach in either the classroom or the clinical environment (e.g., instruction during hospital rounds, patient conferences, primary care settings, ambulatory clinics, emergency departments, etc.). The pharmacotherapy specialist is experienced in behavior modification and communication with patients, peers, and students. When applied appropriately, these skills may result, for example, in improved patient compliance with drugs and altered physician prescribing habits.

Assessment factors

1. Assumes responsibility for the education of all members of the health care team involved in patient pharmacotherapy.

2. Participates in continuing education programs concerning pharmacotherapeutics.
3. Develops patient education materials and participates in patient instruction programs to facilitate appropriate medication therapy and compliance.

GUIDELINE V

The pharmacotherapy specialist continually develops his/her knowledge and skills in applicable practice areas and demonstrates a commitment to continued professional growth by engaging in a lifelong process.

Rationale

The frequent introduction of new pharmacotherapeutic agents into practice, the increasing complexity and technicality of new drugs and biologic products, and the evolution of pharmacotherapy practice necessitate that the pharmacotherapy specialist continually refine, improve, and expand the unique, advanced skills which he/she possesses.

Assessment factors

1. Participates in professional organizations related to areas of expertise, thereby nurturing and enhancing personal knowledge and leadership skills.
2. Increases personal level of knowledge and skills by reading professional journals, and attending or participating in professional seminars, professional symposia, and national and international conferences.
3. Obtains board certification.

ACKNOWLEDGMENTS

Prepared by the 1998–1999 ACCP Clinical Practice Affairs Committee, Subcommittee B: Terry L. Seaton, Pharm.D., BCPS, St. Louis College of Pharmacy, St. Louis, MO; Aileen Bown-Luzier, Pharm.D., Department of Pharmacy Practice, SUNY at Buffalo, Buffalo, NY; Catherine E. Cooke, Pharm.D., BCPS, School of Pharmacy, University of Maryland, Baltimore, MD; John F. DeConinck, B.S., Owen/Cardinal Healthcare Corp., Desert Springs Hospital Pharmacy, Las Vegas, NV; Robert E. Dupuis, Pharm.D., BCPS, School of Pharmacy, University of North Carolina, Chapel Hill, NC; Rex W. Force, Pharm.D., BCPS, Department of Family Medicine, Idaho State University, Pocatello, ID; Peter Gal, Pharm.D., BCPS, FCCP (Chair), Greensboro Area Health Center, Greensboro, NC; Darrell Hulisz, Pharm.D., BCPS, Department of Family Medicine, University Hospitals of Cleveland, Cleveland, OH; Nathan L. Kanous, II, BCPS, School of Pharmacy, University of Wisconsin-Madison, Madison, WI; Dannielle C. O'Donnell, Pharm.D., BCPS, College of Pharmacy, The University of Texas at Austin, Austin, TX; Eric Racine, Pharm.D., Pharmacy Department, Harper Hospital, DMC, Detroit, MI; Theresa Salazar, Pharm.D., School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN; Allen F. Shaughnessy, Pharm.D., FCCP, BCPS, Harrisburg Hospital Family Practice; Harrisburg, PA; Ronald Taniguchi, Pharm.D., Pharmacy Services, Kaiser Permanente, Hawaii Region, Honolulu, HI; and Kay M. Uttech, Pharm.D., BCPS, College of Pharmacy, University of Illinois at Chicago, Chicago, IL.

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PROFESSIONAL DEVELOPMENT

Pharmacotherapy Specialty Practice

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INTRODUCTION

Pharmacotherapy is that area of pharmacy practice that ensures the safe, appropriate, and economical use of medications.[1] The pharmacist who practices as a pharmacotherapy specialist is considered to be an expert in the area of applied pharmacotherapeutics and is viewed as an essential member of the health care team. Similar to the practice of medicine, pharmacotherapy specialists may practice as generalists or may align themselves by specialties (e.g., geriatric medicine, infectious disease medicine, pediatric medicine, oncology medicine, nutrition support, psychiatric medicine). In addition, just as physician hospitalists—specialists in inpatient medicine—are responsible for managing the care of hospitalized patients and primary care physicians are responsible for managing the care of outpatients, a similar analogy may be applied when comparing the pharmacotherapy specialist with the ambulatory care pharmacist. This article focuses on the pharmacotherapy specialist who possesses the set of knowledge, skills, and attitudes specific to the care of hospitalized adult patients and compatible with the diversity of diseases and drugs encountered in the practice of internal medicine. Information on pharmacy practice in outpatient settings or in other types of specialties (e.g., infectious disease, oncology, pediatrics, psychiatry) are not discussed in this article.

FUNCTIONS AND ACTIVITIES

The function and activities of a pharmacotherapy specialist are well described by guidelines published by the American College of Clinical Pharmacy.[1]

Guideline One: *The pharmacotherapy specialist designs, implements, monitors, evaluates, and modifies patient pharmacotherapy to ensure effective, safe, and economical patient care.* The pharmacotherapy specialist takes responsibility for patient outcomes. The pharmacotherapy specialist will use his or her specialized knowledge, clinical observations, analytical skills, and communication skills to work collaboratively with other health care professionals to make decisions that facilitate optimal pharmacotherapy-related outcomes.

Guideline Two: *The pharmacotherapy specialist retrieves, analyzes, evaluates, and interprets the scientific literature as a means of providing patient- and population-specific drug information to health professionals and patients.* The pharmacotherapy specialist should be capable of using their literature evaluation skills to complement their knowledge base and problem-solving skills. The pharmacotherapy specialist optimizes patient outcomes by correctly interpreting the biomedical literature, evaluating its applicability to given patient care situations, and applying when solving drug therapy problems for a given patient.

Guideline Three: *The pharmacotherapy specialist participates in the generation of new knowledge relevant to the practice of pharmacotherapy, clinical pharmacy, and medicine.* The pharmacotherapy specialist has a responsibility to contribute to the generation of new biomedical knowledge and information through research and to share the research results through publication or presentation at scientific meetings.

Guideline Four: *The pharmacotherapy specialist educates health care professionals and students, patients, and the public regarding rational drug therapy.* The pharmacotherapy specialist is uniquely qualified to educate others on the optimal use of drugs. For example, the specialist may provide teaching to health care professionals and students in a classroom setting (e.g., pharmacy curriculum, scientific conference, educational symposium) or a clinical setting (e.g., hospital rounds, hospital clerkships). Education to hospitalized patients usually takes place prior to hospital discharge and may

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DOI: 10.1081/E-ECP 120006236

also focus on nonpharmacologic (e.g., dietary or lifestyle changes), in addition to pharmacologic (e.g., medication education), issues. The pharmacotherapy specialist may also be invited to speak at community health symposiums to educate the public on a variety of pharmacotherapy-related issues (e.g., preventative health medications used to treat various conditions, medication safety).

Guideline Five: *The pharmacotherapy specialist continually develops his or her knowledge and skills in applicable practice areas, and demonstrates a commitment to continued professional growth by engaging in a lifelong process.* As new pharmacotherapeutic agents are introduced into the marketplace and as the practice of pharmacotherapy evolves, the specialist must be capable of continually refining, improving, and expanding their advanced knowledge and skills.

As conceptualized by Holland and Nimmo, pharmacy practice can be categorized into five interrelated practice models (see Appendix).[2] The five interrelated practice models can be simplistically delineated as clinical pharmacy, distributive pharmacy, drug information, pharmaceutical care, and self-care. The value-added functions of a pharmacotherapy specialist often depend on the successful utilization of knowledge and skills derived from three of the five basic practice models—clinical pharmacy, drug information, and pharmaceutical care. Therefore, the pharmacotherapy specialist often has to acquire additional training and education, beyond the level of general licensed pharmacists, that will allow them to provide specialized, value-added functions.

QUALIFICATIONS

The pharmacotherapy specialist is a licensed pharmacist who has received specialized education and/or advanced training in the biomedical, pharmaceutical, and clinical sciences. The pharmacotherapy specialist must also be capable of using sound judgment when practicing pharmacotherapy. The appropriate knowledge, skills, and attitudes of a pharmacotherapy specialist are acquired through academic curricula (e.g., Doctor of Pharmacy program) at an accredited college or school of pharmacy, postgraduate training (e.g., pharmacy residency or fellowship), and/or extensive pharmacy practice experiences.

The pharmacotherapy specialist is generally intelligent and capable of resolving problems that may not have a clear right or wrong answer. They possess a strong sense of responsibility, are confident and conscientious, exercise practicality and logic, exhibit emotional stability and persistence, are able to convey expertise, are socially adept, and possess mature interpersonal skills that are required to successfully participate in collaborative decision making.

P

Certification

According to the Board of Pharmaceutical Specialties,

> *the primary purpose of specialization in any health care profession is to improve the quality of care individual patients receive, to increase the chances of positive treatment outcomes, and ultimately, to improve the patient's quality of life. Specialties evolve in response to the development of new knowledge or technology that can affect patient care, and the resulting changes in patient-care needs. The rapid, dramatic advancement in drug therapy in recent decades has created a clear need for pharmacy practitioners who specialize in specific kinds of treatment and aspects of care. Specialty certification is a responsible, progressive initiative from the profession to ensure the best possible patient care.*[3]

Although not required, a pharmacotherapy specialist may become a Board Certified Pharmacotherapy Specialist (BCPS) through a process established by the Board of Pharmaceutical Specialities (BPS). In addition to pharmacotherapy, the BPS certifies pharmacists in several other specialties (e.g., nuclear pharmacy, nutrition support pharmacy, psychiatric pharmacy, oncology pharmacy).

Recall that licensure to practice as a pharmacist is attained through a government agency after an individual demonstrates a *minimum degree of competency*. It does not indicate that the pharmacist has attained any additional skills or knowledge that is required to practice as a pharmacotherapy specialist. However, successful completion of BPS certification in pharmacotherapy indicates that the pharmacist possesses a level of education, experience, knowledge, and skills that surpass those required to obtain pharmacy licensure.

Additional information on BPS certification can be obtained from the Board of Pharmaceutical Specialties, 2215 Constitution Avenue, NW, Washington, DC, 20037-2985 or online at www.bpsweb.org.

VALUE

A growing body of literature has emerged that supports the value of pharmacist-related activities in improving and promoting the safe, effective, and economical use of drugs.

Researchers from the Harvard School of Public Health, Massachusetts General Hospital, and the Brigham and

Women's Hospital conducted a study designed to measure the effect of a single pharmacist's participation on medical rounds on the rate of preventable adverse drug events in an intensive care unit.[4] The participation of an experienced BCPS was associated with a 66% reduction in preventable adverse drug events and approximately $270,000 in annual cost savings to the hospital. The BCPS was accepted as a member of the multidisciplinary team, and the researchers noted that mutual cooperation and positive interpersonal relationships between the pharmacy and medical staff were vital criteria for successful pharmacist interventions.

In another study, services provided by a pharmacotherapy specialist (e.g., participation on rounds and reviewing of patients' medications) in internal medicine and intensive care units was associated with significant cost savings without negatively affecting the quality of care provided to patients. The drug cost savings alone was estimated at approximately $400,000 per year.[5]

On a daily basis, pharmacotherapy specialists are often involved with many types of clinical pharmacy services and functions associated with added value to patients and the health care system. For example, involvement in cardiopulmonary resuscitation teams, clinical research, drug information services, and medication admission histories is associated with a significant number of lives saved in hospitals within the United States (see Table 1). Six types of clinical pharmacy services—adverse drug reaction reporting, drug information services, drug protocol management, drug use evaluation, medication admission histories, and participation on medical rounds—are associated with an estimated health care cost savings of billions of dollars annually (see Table 2).[6,7]

SUPPLEMENTAL INFORMATION

For additional reading, the American College of Clinical Pharmacy has published a position paper on pharmacotherapy practice.[8] This document may also be viewed online at http//:www.accp.com.

The American Society of Health-System Pharmacists (ASHP) supplemental standard and learning objectives for residency training in internal medicine and pharmacotherapy are published annually by the Accreditation Services Division of the ASHP in the Residency Directory, Volume Two. These documents may also be viewed online at:

http://www.ashp.org/public/rtp/IMSUPPST.html for internal medicine and at
http://www.ashp.org/public/rtp/PHTHSUPP.html for pharmacotherapy practice

Table 1 Clinical pharmacy services associated with reduced mortality rates in United States hospitals

Clinical pharmacy service	Estimated reduction in deaths per year*
Clinical research	201,274
Medication admission histories	131,815
Drug information services	45,428
Cardiopulmonary resuscitation participation team	18,416

*Based on 1029 hospitals that offer these clinical services. (From Ref. [6].)

Table 2 Hospital-based clinical pharmacy services associated with reductions in health care costs

Clinical pharmacy service	Estimated annual cost savings*
Adverse drug reaction monitoring	$1,636,614,476
Drug information services	$5,309,746,272
Drug protocol management	$1,757,282,145
Drug use evaluation	$1,137,727,143
Medication admission histories	$7,075,571,493
Participation on medical rounds	$8,107,395,977

*Based on 1016 hospitals that offer these clinical pharmacy services. (From Ref. [7].)

APPENDIX

Clinical Pharmacy Practice

The clinical pharmacy specialist requires strong skills in designing, recommending, monitoring, and evaluating drug therapy. The ability to convey expertise and persuade prescribers is important. Knowledge of prescription medications and of chronic and acute disease states are important. Their primary role is to help prescribers make appropriate drug therapy decisions. A successful clinical pharmacy specialist must enjoy complex technical problem solving or solving ill-defined problems. In the acute care setting, patient contact may be minimal. However, a high degree of interaction with other members of the health care team (e.g., nurses, dieticians, social worker) is required. In the ambulatory setting, a high degree of patient contact is required.

Distributive Pharmacy Practice

The distributive pharmacy specialist requires strong technical skills in the preparation and dispensing of pres-

criptions, and communication skills to counsel patients on the use and administration of medications. They enjoy technical problem solving and routine activities. Their primary role is to ensure that the right medication gets to the right patient at the right time. Common practice settings include the community pharmacy and the hospital pharmacy.

Drug Information Pharmacy Practice

The drug information specialist requires strong literature evaluation skills, analytical skills, group communication skills, and the ability to persuade prescribers. Their primary role is to provide analytical and educational support to groups of health care providers or the public as a whole. A successful drug information specialist must enjoy researching the scientific literature. This practice does not necessarily involve a high degree of social interaction. Common practice settings include hospitals, managed care groups, and pharmaceutical companies.

Pharmaceutical Care Practice

The ability to provide pharmaceutical care is the profession's ultimate goal. In this practice, the pharmacist shares responsibility and accountability for the patient and drug therapy outcomes. The principal goal of pharmaceutical care is to achieve definite outcomes from medication use that improve the patient's quality of life. These outcomes include cure of a disease, elimination or reduction of disease symptoms, slowing a disease process, prevention of disease, and/or diagnosis of disease. Strong communication skills are required to establish a collaborative relationship with the patient, prescriber, and/or other members of the health care team.

Self-Care Pharmacy Practice

The self-care specialist requires strong skills in health screening, design and recommendation of drug therapy, use of judgment for referrals, and the ability to establish trust with the patient, to convey expertise, and to communicate clearly. Knowledge of nonpres-cription medications and therapy of minor diseases is important. The primary role of the self-care specialist is to help patients make informed decisions about their own care. A successful self-care specialist must enjoy technical problem solving and a high degree of social interaction. A common practice site is the community pharmacy.

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Pharmacovigilence

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INTRODUCTION

The primary goal of pharmacovigilence is to ensure that medications are used to maximal benefit while minimizing the risks of treatment. While clinicians directly involved in patient care seek to provide drug therapy with these same goals, healthcare professionals involved in the field of pharmacovigilence actively monitor the safety profile of medications so as to provide their colleagues directly involved in patient care with the information necessary to use medications in the safest possible manner. The scope of activities that comprise pharmacovigilence is broad, extending from preclinical safety pharmacology work through clinical studies to the "postmarketing" arena. The richest source of safety experience arises once a drug is marketed, yet it remains the most challenging from an analysis perspective. Due to the breadth of sources of safety information, the pharmacovigilence professional draws on a variety of disciplines, including pharmacology, pharmacokinetics, statistics, and pharmacoepidemiology.

REGULATORY ENVIRONMENT

The regulatory requirement that drugs be shown to be safe prior to marketing first became codified in the United States with the Federal Food, Drug and Cosmetic Act of 1938.[1] Prior to that time there was no mandate for an evaluation of drug safety. The Pure Food and Drug Act of 1906 prohibited interstate commerce of adulterated and mislabeled drugs. The Sherley Amendment four years later made it illegal to make therapeutic claims that are false and fraudulent. However, there was no legal basis for establishing that drugs were safe to use. The Food and Drug Administration in 1933 advocated for new legislation that would improve drug safety by illustrating the many shortcomings of the 1906 law. The need for revised legislation became acutely apparent in 1937 after 107 people died as a result of a sulfanilamide product that contained diethylene glycol. The Food, Drug and Cosmetic Act the next year gave the FDA new regulatory authority to require that drugs be demonstrated to be safe prior to commercialization. Since then, the scope of regulations and guidelines applicable to safety surveillance in the Unite States has become extensive.[2,3]

Other countries faced with similar circumstances also enacted similar legislation. Regulations requiring registration of drug products in Japan were enacted in the 1950s. The thalidomide tragedy in 1962 prompted regulatory action in Europe.[4] Across Europe, North America, and Japan this resulted in a panoply of regulations that, while based on the same fundamental goals of safety and efficacy, diverged in their technical requirements. Pharmaceutical companies engaged in the global marketplace found themselves facing duplicative and expensive work in order to meet the various regulations. Regulators in different countries also found it a challenge to exchange safety information when the methods of information collection were not consistent.

The European Community initiated efforts at regulatory harmonization in the 1980s. However, it was during the World Health Organization (WHO) Conference on Drug Regulatory Authorities in 1989 when international harmonization efforts were conceived.[5] The International Conference on Harmonization (ICH) was founded the following year, with industry and regulatory representatives from the United States, Europe, and Japan. The members were given the task to make more efficient the process for developing and registering new medicinal products in the three member areas.

The scope of the resulting ICH guidelines includes safety, efficacy, quality, and multidisciplinary issues.[5] Within the sections on safety, guidelines have been prepared for testing carcinogenicity, genotoxicity, and safety pharmacology, for example. Additional safety issues were addressed in other sections dealing with the expedited and periodic reporting of adverse events, a common nomenclature for describing adverse events, and the extent of population exposure to adequately assess safety. An indication of the success of this organization has been the extent that its recommendations have been adopted by

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006345

various countries worldwide, further improving the steps toward global harmonization.

A number of the ICH guidelines were based on proposals offered by the Council of International Organizations for the Medical Sciences (CIOMS).[6,7] Originally founded by the WHO and UNICEF to produce scientific conferences, CIOMS has since matured into a "think tank" for addressing safety issues faced by both industry and regulators. Like ICH, the CIOMS Working Groups are comprised of members from the pharmaceutical industry and national regulators. Examples of the work of the CIOMS group have been development of a common form for reporting individual cases and periodic summaries of adverse events, elements for electronic data transmission of adverse events, a framework for determining attributability of an adverse event to a drug, and a process for weighing the risks and benefits of a drug product.

INTERNATIONAL ORGANIZATIONS

Additional organizations have developed to foster drug safety. The WHO Department of Essential Drugs and Medicines (EDM), created in response to the thalidomide disaster, established the Drug Safety Programme to communicate information among member states on drug safety and efficacy, including the prompt transmission of serious adverse event experiences.[8] The Uppsula Monitoring Centre, through an agreement with WHO, oversees a collaborative effort among 64 countries, as of January 2000, to monitor drug safety worldwide.[9,10] The Centre's goals are to identify safety risks as soon as possible and communicate them to healthcare professionals and the public in order to facilitate risk–benefit assessments. The WHO program also supports the European pharmacovigilence Research Group (EPRG). The EPRG, established in 1993, is comprised of members from academia and regulatory agencies from 10 European Union member states.[11] The group conducts research and investigations into specific drug safety issues.

CLINICAL DEVELOPMENT

The maturing of the field of pharmacovigilence has led industry and regulators to understand the evolutionary nature of safety surveillance. Whereas much of the impetus for promulgating regulations to ensure public safety was based on problems with commercialized products, a greater appreciation has developed that understanding the safety profile of a medication begins before it reaches the clinic. Safety surveillance begins with preclinical toxicology studies, evolves through clinical testing, and matures with postmarketing experience. Pharmacovigilance groups within pharmaceutical companies take this "long view" of drug safety and put into place systems to address the monitoring and evaluation needs at each phase.

The potential for a new drug or biologic to elicit untoward effects is first examined in preclinical studies.[12] Single-dose and repeated-dose toxicity studies examine the pharmacodynamic effects in at least two mammalian species. Genotoxicity studies examine the propensity of the drug to cause mutations and chromosomal damage. Carcinogenicity studies assess the ability of the compound to produce cancerous changes in cells. The toxic effects on reproductive organs and fertility is examined in reproductive toxicity studies. Untoward effects may first be identified during these initial pharmacodynamic studies. Safety pharmacology studies then seek to further identify adverse effects across a series of organ systems and to define the dose–response curve for these adverse effects. This information forms the initial basis for the scope of adverse effects that might be anticipated in humans.

The first clinical trials of a new compound generally take place in healthy volunteers. These studies seek to establish the initial safety profile in humans and obtain pharmacokinetic information. Up until this point, the extrapolation of the adverse events identified from preclinical studies to humans remains theoretical. Even adverse effects associated with other members of the drug class remain to be demonstrated for the product under study. Emphasis is placed on the clinical investigator to closely monitor the subjects for the development of any adverse effects and to attempt to determine whether a causal relationship exists between the event and the study drug.

The essential elements of pharmacovigilence during clinical trials of an investigational compound span from adverse event identification through characterization and analysis.[13,14] Identification is focused on "treatment-emergent" adverse events. These events can then be characterized by incidence, prevalence, severity, seriousness, and relationship to the study drug (causality). The data can then be examined to identify potential risk factors and markers with which to anticipate the occurrence of an adverse event.

Determination of a causal relationship between the use of a drug and the development of an adverse event can be difficult. A number of algorithms have been developed in an attempt to standardize this process.[15–22] Although each employs elements that are generally accepted, none has been widely adopted in its entirety due to limitations in reproducibility and predictive value. Over time, emphasis has shifted from attempting to assign causality at

the individual case level and instead applying determinations of attributability to aggregate data.

The CIOMS Working Group published a guideline that included considerations of how to approach this assessment. The guideline describes how to create a source of the minimum drug safety information that should be communicated by manufacturers to clinicians, that is, information most needed to help clinicians balance a product's risks against its benefits and thus make good therapeutic decisions. The guideline identifies and ranks 39 factors that can be used to determine which adverse events to include in this "core" safety information document, events that are most likely to be causally due to the use of the drug. Although initially developed from a postmarketing perspective, the CIOMS V and revised CIOMS III report extended the concept of core safety information to the clinical development period prior to marketing.

The accumulating information in the core safety information document serves a number of participants in clinical trials. The investigators brochure, a document detailing the properties of the investigational drug, is augmented by the core document to provide investigators with a sense of the important safety information that can guide their management of clinical trial subjects. The adverse event data in the core document also serves as the basis of the risk section in the informed consent document, the essential adverse events that a subject would need to know about to make an informed decision regarding participation in the clinical trial. This information is also of relevance to ethics review committees (institutional review boards) when assessing the benefits and risks to participants in clinical trials.

Phase III studies are the pivotal trials by which efficacy is established for gaining marketing approval. The larger patient numbers, and often longer duration of drug treatment, in such trials allow for a more extensive evaluation of known adverse events and an opportunity to detect new events present at a lower frequency. The presence of a control group gives pharmacovigilence personnel the opportunity to estimate the baseline frequency rates for adverse events that previously may have been attributed to the drug. Certain adverse events may be secondary to the disease state under study or due to concomitant medication. From the background rate and the observed frequency of the adverse event in the treated group, an estimate can be made of the attributable rate, i.e., the extent to which the drug is causing the adverse event above the intrinsic rate. This information is useful not only in causality assessment but also in determining the magnitude of the effect produced by the study drug and, hence, in making a benefit–risk assessment.

POSTMARKETING ENVIRONMENT

The adverse event experience accumulated during the conduct of clinical trials, in the form of the core safety information document, serves as the basis for product labeling (prescribing information) upon marketing licensure. The safety profile of the drug at this point is characterized by an experiential database numbering only in the hundreds of patients, with limited long-term exposure data. Invariably, adverse events that occur at a low frequency or upon extended use will only emerge when larger numbers of patients are treated. Idiosyncratic drug reactions may also require greater numbers of exposed patients to be detectable.[23] One example of the failure of clinical trials to detect an important adverse event was the cough produced by angiotensin-converting-enzyme (ACE) inhibitors.

The sources of safety information once a drug is marketed can be many. Healthcare professionals using the medication in clinical practice become the frontline for detecting adverse reactions. Spontaneous reports of adverse events to the pharmaceutical manufacturer and/or regulatory authorities is an extremely important source of data for detecting emerging safety signals. Recognizing the importance of this experience, in the United States the Joint Commissions for the Accreditation of Health Organizations (JCAHO) mandates that healthcare organizations maintain a process for the identification, reporting, analysis, and presentation of sentinel events (any unexpected occurrences involving death or serious physical or psychological injury, or the risk thereof).[24] In France and Denmark, reporting adverse reactions that occur in clinical practice is mandated by law. In most other countries, reporting of postmarketing adverse events is voluntary.

The scientific literature is an important source of adverse event information, particularly in the form of case reports. Pharmacovigilence departments routinely scan the published literature for references to their products in order to identify adverse experiences. Case reports and case series can give clues to emerging safety issues. Because of the importance of these experiences, clinicians should publish case reports as soon as possible rather than waiting to assemble a case series.

Pharmaceutical manufacturers may be required to conduct postmarketing safety studies as a condition of drug approval. These may be warranted when licensure is based on limited data submitted for expedited approval or when the safety profile of the drug necessitates additional research. Such investigations can take the form of formal studies or registries, programs where limited but targeted information is collected on a large group of patients.

A significant limitation when analyzing spontaneous reports of adverse events is the inability to calculate frequency rates. In a controlled clinical trial, the number of events (numerator) and the number of trial subjects (denominator) are well known. A frequency rate for the adverse event can be calculated. However, in the postmarketing setting it must be assumed that all adverse events are underreported; hence the numerator value is poorly known and the total number of patients exposed to the drug cannot be definitively established, rendering the denominator value unclear. At best, postmarketing data can be described as reporting rates that cannot be directly compared to the frequency rates arrived at in the clinical trials.

A significant advance in the analysis of safety information for marketed drugs is the availability of large-scale, record-linked databases. These are databases of patient demographics, prescription history, laboratory data, and clinical data that are linked. Health maintenance organizations and academic programs have been instrumental in the construction of these databases, e.g., Group Health of Puget Sound, Kaiser Permanente, and General Practice Research Database. Epidemiologists utilize these systems for case-control studies that can provide estimates of relative and absolute risk. Based on a signal derived from spontaneous reports, for example, pharmacoepidemiologists can use these record-linked databases to explore the validity of this signal in a large patient experience.

The application of epidemiological principles has been a valuable development in the practice of pharmacovigilence.[25] The detection of new adverse reactions is made difficult by their unanticipated nature, delayed presentation, infrequent occurrence, presence of multiple concomitant drug treatments and/or other confounding risk factors. The science of epidemiology brings to pharmacovigilence the concept of risk assessment, tools for making comparisons, and a vocabulary for describing risk. Relative risk provides a measure of the size of an association between drug exposure and an adverse event, which is helpful for establishing associations. The absolute or excess risk is an indicator of the extent to which an adverse event can be attributed to drug use. The epidemiologic principles of relative and absolute risk provide a basis on which these risks can be balanced against anticipated benefits.

RISK–BENEFIT ASSESSMENT

Once a safety signal is identified and analyzed, pharmacovigilence personnel must determine whether it signifies a shift in the relationship between risks and benefits. Weighing the risks and benefits of drug treatment is a fundamental process in clinical medicine. Unfortunately, what appears to be a straightforward process has no agreed-on procedures or quantifiable statistics. Approaches to risk–benefit assessment during development have been published,[26–29] but little work has been directed toward analysis of marketed drugs.

The CIOMS Working Group addressed the task of developing a common approach to risk–benefit analysis in its fourth guidance—CIOMS IV.[7] In addition to providing a standardized methodology for risk assessment, the guidance describes concepts and procedures for determining the magnitude of a safety problem and deciding on appropriate actions. Although not a definitive set of algorithms, the guidance offers pharmacovigilence personnel not only a common schema for approaching risk–benefit assessment but also a recommendation that such common approaches be utilized by industry and regulators alike.

FUTURE DIRECTIONS

The momentum of international harmonization efforts will continue to improve the ability with which adverse events are classified, analyzed and communicated. Paper-based system will be replaced by electronic transmission of adverse event information. The WHO monitoring program will extend the Bayesian artificial neural networks for analysis of the large amounts of adverse event data at its disposal.[30] In the United States, efforts are underway at the FDA to improve the content and format of product prescribing information.[31]

Pharmacogenomics will likely play an increasingly important role in pharmacovigilence as genetic polymorphisms become better understood. Genetic variation can play a significant role in the safety profile of a drug. The science of pharmacogenomics—the study of genetic factors in drug response—has only recently become a viable tool with the advent of sufficiently sophisticated analysis techniques.[32,33] Knowledge of genetic variations in known polymorphic enzymes can help identify genotypes at particular risk. An appreciation that terfenadine metabolism was dependent on a cytochrome P450 isoenzyme (CYP2D6) that was effectively absent in 6–10% of the Caucasian population may have altered the development decisions for the compound or the target population.[32] Such examples of genetic polymorphisms of genes associated with drug metabolism are among the best studied to date. Genetic variants can give rise to unexpected drug effects, e.g., hemolysis in glucose-6-phosphate dehydrogenase deficiency, and variants in the drug target can alter the response and frequency of adverse effects, e.g., variants in the beta-adrenergic receptor can

alter the response to beta-agonists in asthmatics.[34] Mutations in membrane transporters involved in drug absorption can lead to substantial changes in bioavailability. Transporter pharmacogenomics is a rapidly developing field in its own right. As the field of pharmacogenomics matures, it promises to afford a mechanism to improve the safety profile of a large number of drugs.

The process of pharmacovigilence requires the contribution of many healthcare professionals in industry, government, and clinical practice. With improved harmonization, more sophisticated analysis tools, and clearer communication, more patients will be able to realize the benefits of drug therapy while minimizing the attendant risks.

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Pharmacy Benefit Management

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INTRODUCTION

Pharmacy benefit managers (PBMs) are business entities that provide processes and services related to the acquisition and utilization of drugs by customers. They are the technical and clinical conduits for benefit payers (e.g., employers, employer groups, government) to develop, administer, and maintain a pharmacy benefit on behalf of the patients receiving the benefits.

A prescription benefit program is often regarded by consumers as a privilege that accompanies employment. Presentation of a prescription drug card to a pharmacy allows members of a PBM to have prescriptions filled at substantial discount. When filling these prescriptions, most pharmacies interface electronically with the database of the PBM. They then charge the member a copay based on the specific benefit design of their "company-sponsored" prescription program.

Employers share the prescription cost by charging the member a copay. The amount of the copay is typically based on whether the drug is a generic or brand name drug. The copay may also be based on whether the drug is found on a preferred list of medications known as a formulary. Formulary drugs typically are priced more favorably, due to rebate agreements made with the pharmaceutical company supplier. This is reflected in a lower copay when a PBM member's physician writes a prescription for a formulary drug.

PBMs in effect bring about competitive drug pricing. By their management of formularies, PBMs cause competition within the pharmaceutical industry marketplace. They leverage a large client base to negotiate price discounts from drug manufacturers in return for formulary inclusion of the manufacturer's product(s).

Managed care organizations that use PBMs include health maintenance organizations (HMOs), preferred provider organizations (PPOs), government agencies (primarily medicare, medicare plus choice, and state medicaid), and third-party administrators (TPAs). Third-party administrators are organizations outside the insuring organization that handle claims processing, administrative duties, and sometimes utilization review. They are used by organizations that fund the prescription (or total health) benefits, but do not find it cost effective to administer the health plan benefits themselves.

In addition to organized healthcare, private self-insured corporations may also contract directly with a PBM for services. Depending on the size of the PBM and its willingness to work with small groups, contracts may be written for prescription benefit management for small companies. However, many small companies enlist the services of a TPA for representation when it comes to purchasing the services of a PBM.

ORIGIN OF PBMs

Some of the first PBMs originated from managed care, as in the case of Express Scripts.[1] Prescription Card Service (PCS) evolved from an innovative network of community chain and independent pharmacies. The services of PCS were originally the processing of prescription claims for employer groups seeking discounts, and is responsible in large part for the birth of the National Council for Prescription Drug Programs (NCPDP).[2] The NCPDP is an industry group responsible for setting electronic adjudication and prescription submission standards nationwide. In 2000, PCS merged with Advance Paradigm to become Advance PCS the largest PBM at this writing.

The NCPDP helps PBMs standardize online pharmacy claim adjudication. Online adjudication of claims is a key revenue generator for many PBMs. When prescriptions are filled at the pharmacy level, the claim for payment is transmitted electronically to the PBM. At the PBM, computers interface with eligibility data, plan design, and a set of rules that process the claim and send notification back to the pharmacy that the claim is processed. In the case of a rejection, the reason for rejection in the form of a rejection code is sent to the pharmacy. The NCPDP helped the PBMs standardize the data files used to adju-

DOI: 10.1081/E-ECP 120006334

dicate claims and the codes used to submit utilization data for formulary drug rebates.

Diversified Pharmaceutical Services, Inc., with roots going back to the early 1970s, is credited for establishing maximum allowable cost (MAC) programs and mandatory generic drug programs.[3] It has been associated with SmithKline Beecham Healthcare Services and was once a subsidiary of the United HealthCare Corporation, but is now part of the Express Scripts network.

Actual ownership of the PBMs varies. Some companies are privately held corporations (e.g., National Prescription Administrators). Some are publicly traded (e.g., Express Scripts). Some are now or have been owned by managed care organizations (e.g., PacifiCare's ownership of Prescription Solutions or Prudential's ownership of Integrated Pharmacy Solutions). They have also been owned by retail pharmacy chains, as in the case of Rite Aid's ownership of PCS prior to its evolution into Advance PCS. Pharmaceutical manufacturers have purchased PBMs (e.g., Merck owns Medco and Lilly at one time owned PCS).

INITIAL MANAGED CARE CHALLENGE: COST

In the 1990s, both utilization and overall cost of pharmaceuticals increased drastically. This allowed cost containment programs and the PBM business to flourish. The annual percent change in retail prescription prices rose significantly higher than the consumer price index. Marketplace entry of new, higher-priced medications and direct to consumer marketing of medicines contributed significantly to increased patient utilization. Analysis of the recent explosion of drug prices is beyond the scope of this chapter; however, a sobering fact to note is that national health care expenditures for prescription drugs totaled $91 billion in 1998. This is expected to reach about $243 billion in 2008.[4]

The annual percentage increases in prescription expenditures have surpassed all other components of personal health care expenditures in the past decade. Yet, growth in expenditures and prescription drugs still comprise a relatively small proportion of total health care costs.

ONGOING MANAGED CARE CHALLENGE: BUILD OR BUY YOUR PBM

Typically, PBMs charge a managed care organization by the number of prescription claims administered. Plans with low to moderate levels of membership can realize substantial savings by outsourcing the services of a PBM. For example, a plan with 100,000 members who use their benefit averaging 0.7 prescription claims per member per month at 60 cents per claim would be billed $42,000 per month. Compare this with the cost of building a plan with an in-house pharmacy program staff, which could run into the hundreds of thousands of dollars.

The question that must ultimately be answered before contracting with a PBM is whether doing so will yield drug cost savings. Managed care organizations considering contracting for PBM services must compare the cost of the potential PBM contact with the cost of building an internal pharmacy program. For many organizations, purchasing the services of an established PBM (with its attached clinical expertise) makes better business sense than building one internally.

In addition, PBMs can assist with many of the challenges facing managed care organizations in the administration of a prescription drug program. These challenges may include

1. *Administering multiple plan designs and copayments.* Managed care organizations will inherently differ in the way their plans are designed. For example, a step therapy program for the treatment of hypertension may be part of one organization's design, but not anothers. An assertive PBM can set both prescribing protocols for the physicians as well as produce policies for prescription processing with regard to copay levels.
2. *Performing audits of contracted pharmacy providers (e.g., retail pharmacies contracted to provide pharmacy services).* This is done to ensure that both the PBM and the managed care organization (payer) are being charged properly by the dispensing pharmacy for what is actually dispensed to the patients.
3. *Adjudicating claims electronically.* This refers to the actual transmission of a prescription claim via telephone lines from the pharmacy to the PBM database. Various benefit design rules are applied to the electronic claim as it is processed. This processing or adjudication step is an expensive item and can be administered on a cost per claim basis. Depending on the number of covered patient lives within a prescription plan, economies of scale may prevail, allowing for a low cost per claim adjudication fee to be offered to large plans. As the reader may imagine, cost per claim is a competitive area among marketers of PBM services.

4. *Providing Drug Utilization Review (DUR) edits.* These are electronic messages transmitted back to the dispensing pharmacist when filling a prescription. These edits provide messages concerning many aspects of drug therapy, and can flag nonformulary drugs when attempts are made to fill them. The DUR message from most PBMs alert the pharmacist to preferred drugs in lieu of the nonformulary drug being considered for dispensing. The National Drug Code (NDC) number flagging or blocking at the point of dispensing is a common function of DUR edits. Other parameters may be programmed into DUR edits by a PBM. For example, age limit parameters may be used for certain NDC numbers. Cosmetic (e.g., retinoic acid) products or attention-deficit disorder drugs may be excluded from coverage in patients over a certain age. Entire therapeutic category exclusions can be managed by DUR edits as well. For example, the oral contraceptive or fertility drug class prescriptions can be programmed for DUR flags. However, DUR edits can be patient friendly. Drugs that require a prior authorization can be logged into a patient's drug coverage profile. Once authorization is complete for the initial filling, subsequent refills can be approved electronically by means of DUR edits.
5. *Introduce initiatives on behalf of drug manufacturers to support the goals of a managed care organization.* This may take the form of unrestricted grants, promotion of internal health fairs, and wellness programs. For example, the manufacturer of cholesterol medicine may support health initiatives of a managed care organization aimed at reducing heart disease. A PBM can often be a valuable conduit for this type of support.
6. *Communicating prescription benefits, formulary drug lists, utilization management, and disease management initiatives to physicians and to patients.*
7. *Negotiating the contracted drug reimbursement rates for network and mail service pharmacies.* Some PBMs use a MAC pricing schedule for generic drugs, limiting the pharmacist's reimbursement rates, and thereby containing cost for the health plan payor.
8. *Maximizing cost savings by sharing savings from pharmaceutical contracts with the managed care organization.*
9. *Ensuring competitive administrative fees associated with prescription claims and management reports.* Competition in the marketplace puts pressure on the PBM to offer a managed care organization a fair and equitable rate on the prescription claims processed by the PBM. As a service not unlike others in health care, fees charged by PBMs are negotiable and should provide value to the managed care organization.

Once hired by a managed care organization, the PBM must also report utilization trends back to the organization. These reports must be meaningful in a way that will provide the managed care organization with data from which to draw informed conclusions as to how it is spending its prescription drug dollar.[5]

PBM ACTIVITIES

A number of products and services beyond the collection and processing of pharmacy prescriptions are offered to customers by PBMs. The following paragraphs, although not complete, provide a listing of some of the many services offered by PBMs.

Claims Adjudication/Processing

A claim is a bill, generally submitted electronically in a standardized NCPDP format (NCPDP), for products and services rendered by retail pharmacies. Once received, the claim is audited via a series of programs that make up the adjudication process. The information is scrutinized for appropriate content, correctness, eligibility, pharmaceutical, and benefit appropriateness. Real-time electronic point-of-sale claims are adjudicated according to the plan design of the patient's benefit. The technology used allows for the data to be merged with eligibility and pharmacy data pertaining to each member and plan. The adjudication process also provides electronic messaging for ease of prescription filling by the pharmacist. (The message received is guided by the results of the various adjudication programs.) The goal of this messaging is to foster plan/formulary compliance and ultimately bring about cost efficiency for payors.

There are 12 basic audit steps in the adjudication process (Fig. 1). They are as follows:

1. *Submit claim*—The pharmacy sends the claim electronically to the PBM responsible for processing, as indicated by the patient's benefit card.

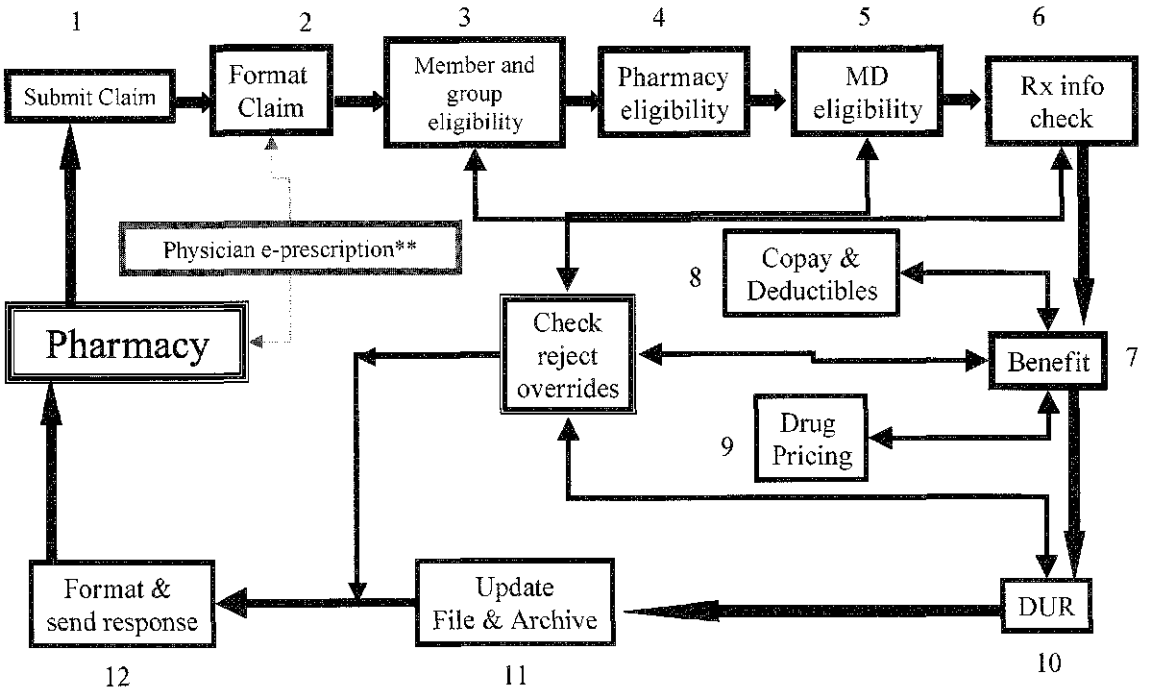

Fig. 1 PBM claim adjudication process.

2. *Format claim*—Claim information is inserted into appropriate fields of the NCPDP standard format.
3. *Member and group eligibility*—The patient/member information is checked against a current list of patients eligible to receive a medical benefit. The type and extent of the benefit received is indicated by the "group" to which the individual belongs (e.g., all employees of a single company usually make up a "group").
4. *Pharmacy eligibility*—Not all medical benefits include coverage of pharmaceuticals. The member/patient information must be checked against a list of individuals eligible for a pharmacy benefit (e.g., currently medicare beneficiaries do not receive a pharmacy benefit; thus, no assistance is offered in the coverage of pharmaceutical costs).
5. *MD eligibility*—The prescribing physician is checked against a list of approved health plan providers.
6. *Prescription information check*—Once the prescription information is placed in the proper format, each piece of information is checked by a program for agreement with the other components of the prescription information (e.g., drug selection agrees with NDC number, drug agrees with the dose, dose agrees with the dosing schedule, quantity agrees with day's supply).
7. *Benefit*[6]—This indicates what medications are covered and under what circumstances. The benefit is defined by the degree to which the patient will contribute to products and services via a copay. The entity that provides the benefit quantitates and determines the benefit limits (e.g., if the benefit is provided to the patient by the employer, then the employer dictates the conditions of the benefit—for example, "lifestyle drugs" that offer cosmetic improvement may not be covered in favor of covering critical medications that treat disease).
8. *Copays and deductibles*[6]—These are the prescribed dollar contributions that the patient must pay to receive a particular pharmacy product or service. The prevailing logic for copays is that increasing the patient's share of the cost will encourage the patient to influence prescribing. If the patient must pay a higher copay, then the patient may influence the physician to seek

lower copay (less costly to the health plan) drugs. Thus, copays are used indirectly to steer a physician's prescribing habits. Copays are also used to encourage patients to request the generic version of medications when available (e.g., a patient benefit may state a low copay of $5 for a generic medication, $10 for a brand name medication, and/or $25 for a nonformulary medication).

9. *Drug pricing*—The prescription information is matched with a listing of per unit price, as dictated by PBM purchase contracts with pharmaceutical companies.
10. *DUR*—This process can take many forms depending on the goal to be accomplished. The drug can be scrutinized against the existing patient profile for drug interactions, accuracy of dosing, and/or prescribing instructions or duplicity. The purpose is to ensure appropriate prescribing for the most common or majority use. It is not intended to check appropriateness for clinical exceptions to "the rule." Actions to be taken, if any, are relayed back to the pharmacy by an edit message. The edit message may indicate that the prescription will not be covered until discrepancies are corrected or further information is given. The DUR message is one of the vital communications between the PBM and the dispensing pharmacy. The actual DUR message can suggest a preferred formulary drug for a particular nonformulary drug submitted. The DUR message may be in the context of an interaction warning or overdosage warning supplied by the logic of the PBM's internal software. Discrepancies between quantity and day's supply violations may be communicated back to the dispensing pharmacist as well. For example, a pharmacy may enter correct information for a birth control prescription. If the patient file indicates the patient is female and that birth control is part of the allowable benefit, then the prescription will be covered with a copay. If the patient's file indicates the patient is male, a rejection code will be generated with an appropriate message sent back to the pharmacy.
11. *Update file and archive*—The patient's drug profile and the PBM's data archive are updated to reflect the latest information. The information necessary to complete the transaction is sent electronically back to the pharmacy. Updating a patient file ensures a continuous, accurate prescription record. This record can then be checked for compliance, drug interactions, compared with medical claims to check for appropriateness of treatment, etc., all of which offer opportunity for the pharmacist, physician, or PBM to avoid an adverse event or improve a clinical outcome.
12. *Format and send response*—The adjudicated claim is returned to the dispensing pharmacy. The industry standard for claims communication is National Council for Prescription Drug Program (NCPDP) formatting. With this format, the various field containing characters and text are standardized and easily recognizable to pharmacies. This final link will clarify such parameters as:

    - patient identification
    - ingredient cost(s)
    - days supply of medication
    - copay due from patient
    - dispensing fee
    - final amount reimbursed to the dispensing pharmacy

Retail Network Access

PBMs have contractual relationships with retail pharmacies and share a common electronic network. Through this common network, prescription claims can be sent to a common point of collection (the PBM). Large PBM–retail networks offer customers easy access to prescriptions throughout the United States. Network relationships are less costly to PBM customers due to volume discount and greater billing/payment efficiencies (e.g., all pharmacies that contract with the PBM are part of that PBM's pharmacy network).

Mail Order Services

Providing volume discounts and less administrative cost to the payer, by virtue of making payments to only one business, makes mail order a cost-efficient alternative. Patients are often incentivized to use mail order services with offerings of home delivery, discontinued multiple-month supplies of medication, and discounted copayments.[6,7]

Account Management

PBM representatives act as liaisons with the purchaser of pharmacy benefits for the purposes of exchanging information on benefit utilization, collaboration on health education or interventional programs, maintaining and updating the benefit as needed, and addressing patient needs and satisfaction issues. PBM representatives and purchasers also collaborate to ensure that quality pharmaceuticals and services are delivered at minimal cost. Good disease management translates into greater productivity and less absenteeism for the employer. Thus employers have a vested interest in improving the health of their employees. An employer with a young covered population—young men, women, and children—would have concerns that medications for diseases predominant in the young, like asthma, would be adequately covered by the benefit and used appropriately by patients. Account managers work with employers to create ways to meet these health goals.

DUR/DUE (Drug Utilization Evaluation)

PBMs offer analysis of drug utilization patterns at both individual and group levels. From these analyses, they may recommend an intervention, education, or course of action to ensure appropriate utilization and outcome. DUR/DUE edits also occur online as the prescription is processed. If the prescription information does not match program criteria for appropriateness, an edit message is generated to the filling pharmacy.

Formulary Management

PBMs undergo a continual process of evaluating individual drugs, drug classes, and their application in disease. The process includes the use of internal and external medical and pharmaceutical expertise to evaluate the efficacy, safety, and cost of pharmaceuticals in the context of their use in a variety of disease states. This process provides for continual improvement of the pharmacy benefit as new products come to market. In addition to an ongoing evaluation of the value and application of formulary drugs, PBMs negotiate contracts for these drugs. Contracts are negotiated in consideration for a PBM placing a partciular particular manufacturer's medication on a preferred drug formulary. Contracting with the pharmaceutical industry allows revenue to flow into the PBM and ultimately back to the PBM's clients. This in effect brings about discounting of pharmaceuticals.

Disease Management

PBMs evaluate prescription data to identify drug/disease patterns of use, and develop programs targeted to ensure correct dosing, compliance, and maintenance of treatment standards are maintained. Disease management programs may originate from within the PBM or may be outsourced to a specialty company with this expertise. Generally, pharmaceutical manufacturers assist PBMs with their disease management initiatives.

Utilization Reporting

PBMs offer aggregate reports from their prescription data archives. These data are stripped of all patient-identifying information and are disseminated to physicians or employers for the purpose of enhancing patient outcomes. PBMs offer the expertise of clinical pharmacists to assist in the interpretation of aggregate reports. Clinical pharmacists help identify trends and goals to set for maximization of patient outcomes.

Patient Education

PBMs offer educational services to patients in many forms. These may include newsletters, specialty programs, advice lines, consultation services, and internet-based information services, and so on.

Customer Support

PBMs offer services to both customers and benefit purchasers to ensure that questions are answered and problems are resolved in a timely manner.

Prior Authorization

The purpose of prior authorization is to safeguard the appropriate use of specialized or niche drugs, drugs with potentially serious toxicities or narrow therapeutic index, and very costly medications. This step requires that additional information be given before the drug in question will be paid for by insurance. Information requirements necessary to receive authorization for coverage of a particular drug may include previously failed drug therapies, requirement of certain diagnostic tests, and complications of disease.

Benefit Development

PBMs offer expertise in designing the most appropriate and cost-efficient benefit based on a number of demo-

graphic parameters to include prevalence of disease, age of the insured population, and cost limitations.

TRENDS

The business of medicine and of managed care is ever evolving. The PBM industry is continually challenged with issues surrounding the development of new treatments and technologies. Listed here are a few of the PBM trends of the future.

Four-Tier Formulary Design

A tiered benefit is a type of pharmacy benefit that has grown in popularity in recent years. Rather than follow the "traditional" formulary process of selecting "best in class" medications for formulary inclusion, a tiered benefit simply stratifies medications according to some basic parameters, usually efficacy, safety, and cost. This design of benefit usually does not preclude the coverage of any given medication (as with the traditional closed formulary design) but rather allows for a greater cost sharing by the patient. Medications in lower tiers are usually available as generic, possess a clinical advantage of some type, or are more cost-efficient. Medications placed in higher tiers are usually those that offer no clinical advantage, are more expensive, or are "lifestyle enhancing" in nature (e.g., medications for sexual performance, cosmetic drugs, fertility agents, hair restoration drugs, appetite suppressants, oral contraceptives).

Traditionally, pharmacy benefits have been of three-tier design; each tier associated with an ever-increasing copay (e.g., 1st tier, $5; 2nd tier, $10; 3rd tier, $25) for common medications. Under this design a few select medications, such as "lifestyle-enhancing" drugs, were either not included in the benefit or were severely restricted.

Consumer demands for greater access to medications has prompted the development of a fourth tier. This differs in that it introduces the concept of coinsurance, or percentage copay to consumers. Medications in this tier would be covered as a percentage of total medication cost as opposed to a set copay amount. For example, fertility medications might be covered at 50% of their total cost. The patient would pay 50% and the pharmacy benefit would pay 50%. Thus providing the consumer and the physician with an incentive to discuss considerations of cost.

Electronic Prescribing

Electronic prescribing has been a much sought after goal by the health care industry. Electronic prescribing would close many of the loopholes through which medication errors often pass. By eliminating the handwritten word, e-prescribing would significantly reduce errors in prescription interpretation; can allow for real-time drug screening, formulary, and DUR checks; and streamline the communication process between the HMO, pharmacist, and physician.

Barriers to electronic prescribing generally circulate around issues of connectivity and ease-of-use issues with physicians, and the cost of implementing this technology in both physician practice and pharmacies. For a seamless system to work, the prescribing physician must have

1. *Ready access to benefit information.* What is the formulary, and what if any conditions must be met for coverage?
2. *The Benefit provider information.* Who is the HMO/PBM benefit provider?
3. *A Common electronic interface.* Will a single program interface with all benefit providers? Will it interface with all retail pharmacy providers? How will the prescription information get to the correct provider? What devices will physicians use to interface with the system? Computers, handheld devices?

Although the benefits to the patient and the health care marketplace would be tremendous, there are many obstacles to overcome. One market development holds great promise for bringing the health care system one step closer to making e-prescribing a reality: On February 22, 2001, three of the largest PBMs, Advance PCS, Express Scripts, and Merck–Medco announced an agreement to establish a common utility for the collection of prescription information. The company, known as RxHub LLC, will act as the central "conduit of information between all parties" and "will provide a single standardized channel of communication to link physicians through electronic prescribing software on their handheld computer or practice management system to pharmacies, PBMs and health plans."[8] The success of e-prescribing and of ventures like RxHub holds great promise for increasing efficiency.

Potential Regulation of PBMs

Due to their inherent activities, PBMs are alleged to be involved in the practice of pharmacy by some lobbying groups. As a result, the National Association of Boards of Pharmacy has advised each state board of pharmacy to evaluate and license PBMs in their area. The Academy of

Managed Care Pharmacy disagrees with PBM licensure, claiming that a very small percentage of PBM activity could be defined as practicing pharmacy. Legislation has been proposed by various state legislatures to license PBMs as pharmacies. Licensing legislation most probably will take the form of a separate class of pharmacy licensure. Separate licensing would in turn lead to potential state regulation of PBMs. Georgia, for instance, has signed into law a bill that mandates the licensure of pharmacy benefit managers doing business within the state. This licensure requirement allows for inspection of pharmacy benefit managers by state inspectors.

Another regulatory issue is therapeutic interchange of medications. PBM clinical departments often set up internal protocols for alternate product substitution within a therapeutic class. The National Association of Boards of Pharmacy contends that therapeutic substitution is practicing pharmacy. In one of its position papers, the Academy of Managed Care Pharmacy supports the use of therapeutic interchange programs. The Academy of Managed Care Pharmacy contends that this decision is ultimately that of the physician.[9]

Another form of regulation now facing PBMs is in the form of the Health Information Portability and Accountability Act. This enormous set of regulations, which is expected to have full legal effect in the near future, would potentially affect not only the processing of confidential patient information, but also the administration of other clinical programs (e.g., disease management, formulary management, drug compliance programs, patient and clinician education programs).

ACKNOWLEDGMENTS

Paul Hueseman, PharmD, Medical Information Scientist, National Accounts, AstraZeneca Pharmaceuticals, and Ben Sloan, National Account Director, Salix Pharmaceuticals.

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Pharmacy in the 21st Century

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INTRODUCTION

Since 1984, four Pharmacy in the 21st Century conferences have occurred. Each conference sought to provide a current and future assessment of the pharmacy profession and healthcare.

1984: THE FIRST CONFERENCE

The first Pharmacy in the 21st Century Conference[1] was held March 25–28, 1984, in Millwood, Virginia. The conference was sponsored by several pharmacy and trade associations, pharmaceutical companies, the Institute for Alternative Futures, and the Institute for Health Policy of Project HOPE. Over 50 representatives from the sponsoring associations, the pharmaceutical industry, and other healthcare professions participated.

The conference focused on the future of pharmacy and its role in healthcare over the next 25 years. The mission of the conference was to consider such issues as the nature and quantity of healthcare and pharmaceutical services, total drug volume, classes of drugs, pharmacy functions, practice locations, and pharmacy personnel needs. Fourteen leaders in healthcare gave presentations on different issues affecting pharmacy's future. The participants discussed the changes in pharmacy practice and imagined what pharmacy would be like in 2010.

Work groups identified several trends for the future. Major factors expected to affect pharmacy included a growing elderly population, more health promotion and wellness activities, increased efforts to prove the cost effectiveness of drugs, a decline in healthcare expenditures as a proportion of the Gross National Product, and an increase in nontraditional therapies. There would be more sophisticated drug delivery systems, and more prescription drugs would become available on a nonprescription basis. Finally, it was believed that pharmacists would play a greater role in monitoring medications and that most pharmacists would practice within large healthcare systems or chain pharmacies.

1989: THE SECOND CONFERENCE

The second Pharmacy in the 21st Century Conference[2] was held October 11–14, 1989, in Williamsburg, Virginia. This invitational conference was sponsored by seven pharmacy associations and nine other groups. The conference had 108 participants, including pharmacy leaders, pharmacy practitioners, and representatives from consumer groups, government, and healthcare administration.

The objective of the conference was to identify the critical issues facing the pharmacy profession in the next 15 to 20 years. Keynote speakers described trends relating to public policy, technology, healthcare economics, and healthcare delivery. C. Douglas Hepler, Ph.D. presented an address coauthored by Linda M. Strand, Pharm.D., Ph.D. on pharmacy's opportunities and responsibilities in healthcare. This presentation was a milestone for pharmacy and defined "pharmaceutical care" as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life."

The consensus statements that were drafted identified several needs in pharmacy: Create a mission statement, develop standards for pharmacists to apply in managing pharmaceutical care, demonstrate and communicate the value of pharmaceutical care to healthcare, measure the quality and outcomes of services, strengthen political action, and convince the public and payers of the benefits of pharmaceutical care. The obstacles facing practice were also noted. The overarching conclusion was that pharmacy had to actively demonstrate and communicate its value to healthcare.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006195

1994: THE THIRD CONFERENCE

The third Pharmacy in the 21st Century Conference[3] was held October 7–10, 1994, in Lansdowne, Virginia. This invitational conference was organized and sponsored by the Joint Commission of Pharmacy Practitioners, a consortium of national pharmacy associations and liaison organizations. Members of JCPP included the Academy of Managed Care Pharmacy, the American Association of Colleges of Pharmacy, the American College of Apothecaries, the American College of Clinical Pharmacy, the American Pharmaceutical Association, the American Society of Consultant Pharmacists, the American Society of Health-System Pharmacists, the National Community Pharmacists Association, the National Association of Boards of Pharmacy, and the National Council of State Pharmacy Association Executives. The conference had 131 participants, including pharmacists and representatives from the sponsoring organizations, medicine, nursing, and public and private agencies.

The objective of the conference was to understand and overcome the barriers to delivering pharmaceutical care in all settings. The two keynote speakers were David A. Zilz, who presented "The Changing Health System: Implications for Pharmaceutical Care," and Carl E. Trinca, who presented "The Pharmacist's Progress Toward Implementing Pharmaceutical Care." A panel of five pharmacists representing hospital pharmacy, long-term and specialty care, managed care, and independent and chain practice described the services they provided and how they overcame obstacles to providing pharmaceutical care. These presentations set the stage for work groups to identify barriers to implementing pharmaceutical care, the reasons for those barriers, and strategies for overcoming the barriers and implementing pharmaceutical care in community and ambulatory care, hospital and institutional care, long-term care, home healthcare, and managed care.

Work groups classified the barriers as economic, educational, political and legal, technological, and social, interprofessional, and intraprofessional. The work groups also proposed strategies for addressing these problems in each practice setting. It was concluded that pharmacists should direct their attention to patients, acquire the skills needed to provide pharmaceutical care, collect and share patient information, document the services and care provided, perform and participate in outcomes research on pharmacists' interventions to demonstrate the clinical and economic value of pharmaceutical care, and recognize that new credentials will be developed for pharmacists providing high-quality patient care.

1999: THE FOURTH CONFERENCE

The fourth Pharmacy in the 21st Century Conference,[4] "Reengineering the Medication-Use System," was held October 1–3, 1999, in Baltimore, Maryland. This invitational, interdisciplinary conference was organized and sponsored by the Joint Commission of Pharmacy Practitioners and had 108 participants from pharmacy, medicine, and nursing. Also included were benefit managers and representatives from federal regulatory agencies, consumer advocacy groups, the pharmaceutical industry, the information systems industry, and the health insurance industry.

Instead of focusing strictly on the pharmacy profession, the fourth conference addressed the quality of the entire medication-use system. The objectives were to describe—and publicize—the extent of preventable morbidity, mortality, and excess costs resulting from suboptimal medication use; to stimulate discussion of the social and economic impact of dysfunction in the medication-use system; to develop a reengineered system for medication use that would optimize clinical, economic, and humanistic outcomes; to identify strategies that could be used to evaluate and implement the models developed; and to foster greater interprofessional collaboration and a shared commitment to optimal medication use.

Several keynote presentations set the stage for workshops focusing on opportunities for improving the medication-use system; recommendations for applying technology and preventing human error; recommendations for medicine, nursing, and pharmacy; and strategies for improving the medication-use system. The final exercise was the development of recommended strategies for reengineering the medication-use system. These included improving the clinical decision-making process related to medication use; improving communication among health professionals and between health professionals and patients; ensuring safety in drug distribution, dispensing, and administration; and educating individual patients and the public about responsible medication use.

DISCUSSION

Each Pharmacy in the 21st Century Conference had a different focus yet each had a positive impact on the profession and on healthcare. For instance, the concept of pharmaceutical care—a major milestone for pharmacy—was widely introduced as a result of the second conference. Since that time, pharmacists have been increasingly recognized for what they do: helping people make the best use of medications.

The series of conferences helped the profession to evaluate pharmacy practice and move forward. In addition, they provided a platform for pharmacy to work with other healthcare professions, healthcare administrators, consumer groups, and public and private agencies.

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Placebo Effects

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INTRODUCTION

The definition of placebo and its role in medicine have changed dramatically over the past 50 years. Prior to 1945, *placebo* was defined as an inactive substance given to appease the patient rather than for medical purposes.[1] Lack of a definitive diagnosis or treatment often resulted in the use of an inert preparation (e.g., sugar pills, colored water) to treat the patient. These agents were given for peace of mind without medical consequence and their efficacy separated imaginary symptoms from those secondary to disease. In the 1950s, widespread acceptance of clinical trials to determine safety and efficacy of drug therapy led to the need to assess the therapeutic effectiveness of the *placebo*. The double-blind, randomized, placebo-controlled, clinical trial design was developed to standardize medical research, decrease physician and patient bias, and account for changes secondary to the natural history of disease. Clinical outcome was considered significant only if response in the experimental group was superior to that in the placebo group. It was confirmed that a certain percentage of patients improved with placebo therapy.

In 1955, Beecher attempted to quantify the placebo response in 15 randomly selected clinical trials encompassing a wide variety of ailments (e.g., pain, cough, behavior changes).[1] Of the 1082 patients receiving placebo, 35.2% experienced therapeutic benefits.[1] Response was noted regardless of the intelligence of the person. Further, patient beliefs, habits, and educational background appeared to be consistent within those who responded to placebo.[1]

The ethical use of placebos as the gold standard to establish efficacy and safety of new agents in clinical trials has recently come into question. In order to establish efficacy of antiretroviral therapy in decreasing placental transmission of HIV, the HIV-infected pregnant females in Thailand and Uganda received placebo therapy, despite the known efficacy of zidovudine in decreasing placental transfer. Concern regarding the use of placebos when effective antiretroviral therapies are available led to the recent revision of The Declaration of Helsinki. The Declaration of Helsinki, produced in 1964 by the World Medical Association, has been the primary document describing ethical practice in medical research. The original doctrine was developed to set international standards for human experimentation after World War II. The Declaration of Helsinki has no legal authority; therefore, it is the role of the investigational review board (IRB) to set and enforce the standards for the ethical participation of humans in medical research at each institution.

PLACEBO EFFECT/RESPONSE

Placebo therapy encompasses any therapeutic intervention or treatment for which no scientific theory including mechanism of action, the effect of administration, and/or a medical act has a specific effect on the condition for which it is prescribed.[1–3] It is distinct from the natural history of disease. When used appropriately, it can idetify the variation due to nonspecific effects such as physical setting, informed consent process, cultural background and equivalence of participants, differences in healing rates, patient or provider bias about treatment, characteristics and communication skills, and perception of the practitioner by the patient.[4,5] Placebo use is further divided based on the agent or therapy administered into two groups: pure and impure placebos.[2] Pure placebos do not possess pharmacologic activity (i.e., contain lactose and normal saline), while impure placebos possess pharmacologic activity irrelevant to the disease under study.[2]

Placebo effect or placebo response has been referred to as the lie that heals.[2] It is the change in patient condition due to a symbolic intervention and increased awareness (e.g., consultation, procedure) rather than pharmacologic or physiologic intervention. It is used to eliminate observational bias in many clinical trials.[2] Elements of placebo response exist in almost every patient encounter. Variables that have been shown to affect patient outcomes

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DOI: 10.1081/E-ECP 120006393

include method of recruiting, the informed consent and consenting process, procedures for blinding, vehicle delivery (brand of medication, capsule color, size, preparation, consistency of the product, and equivalence to the medication being compared), and patient-specific factors (preexisting conceptions and beliefs).[6–8]

The method of patient recruiting, consenting, and blinding has been shown to influence patient beliefs and subsequent reporting of efficacy and safety of the medication.[4] Means and type of vehicle delivery appear to affect patient perception of intervention strength, and adverse events.[8] One study found that increased confidence in the manufacturer appeared to supplement relief obtained in both placebo and active medication groups.[6]

Patient beliefs and attitudes have the most influence on outcomes, and reporting of efficacy and adverse events. When patients are provided with information, emotional support, and an intervention consistent with preexisting conceptions, a sense of control over their illness and positive response to therapy were achieved.[2] The expectation from the drug had an influence on the magnitude of the response.[9]

PLACEBO RESPONSE IN VARIOUS DISEASES

Over the past 50 years, placebo-controlled trials have been used by practitioners and researchers to determine the efficacy and safety for a variety of therapeutic interventions. In all clinical trials regardless of disease state (e.g., peptic ulcer disease, ulcerative colitis, dental pain management, hypertension, hypercholesterolemia, migraine) or therapy received (e.g., antacids, clofibrate) patients exhibited placebo response (Table 1). The extent of placebo response (subjective and objective measures) varies between trials and disease states. Evaluation of the literature demonstrates the extent and variety of factors implicated in response. Faizallah et al. studied the effects of high- and low-dose placebo versus high- and low-dose antacids in the treatment of peptic ulcer disease.[10] Patients with more significant disease received high-dose placebo versus high-dose antacid therapy. Those with less severe disease were given low-dose placebo versus low-dose antacid therapy. Response appeared to be dependent on the agent received and extent of the underlying disease. Patients in the low-dose placebo group reported a 35% response while those receiving high-dose placebo reported a 13% response to therapy.[10] This suggested that patients with more severe disease were less likely to demonstrate a placebo response. However, poor compliance (2/3 of the desired used volume) among the patients receiving high-dose placebo may account for the decreased response.

Placebo therapy in the treatment of ulcerative colitis has consistently shown a measurable benefit. Ilnyckyj et al. reviewed the literature to determine the extent of placebo response in the treatment of acute ulcerative colitis.[11] Analysis of all double-blind, placebo-controlled trials of patients with active ulcerative colitis by multiple reviewers ensured appropriate data extraction and a series of analysis were conducted on the various clinical, endoscopic, and histological endpoints. Remission (10%) occurred less frequently than response (30%) with placebo therapy. Number of patient visits appeared to be related to placebo response (clinical, endoscopic, and histologic) but not remission. Therefore, the authors concluded that conditioned response with active intervention may have a significant effect in placebo response.

Understanding endogenous mechanisms may account in part for the placebo response in patients with pain. The release of endorphins (endogenous opiate-like substances) is believed to mediate the response to pain.[12] Naloxone, a pure opiate antagonist, should block the effect of endorphin analgesia that is often quantified as placebo response.[12] Patients who received naloxone post dental extraction experienced more pain compared to placebo responders. The placebo response was attributed to endorphin release.[12]

The mechanism of placebo response in blood pressure is not well understood. In a study of 1292 stage I and stage II hypertensive females, 30% responded to placebo therapy.[13] Response varied with age and ethnicity. The response in elderly Caucasian females was greater than in other age and race subgroups, 38% versus 23–27%, respectively.[13] Factors such as natural history of the disease and regression to the mean have been suggested as the basis for this placebo response.

Placebos have been useful in determining the efficacy of various therapies in decreasing mortality and morbidity. The Coronary Drug Project Research Group evaluated the efficacy and safety of several lipid-lowering drugs such as clofibrate on the long-term morbidity and mortality of patients with coronary artery disease.[14] Subgroups defined by patient response were determined after randomization. Patient adherence of 80% or greater appeared to substantially lower five-year mortality in both the clofibrate and placebo groups.[14] Factors such as patient adherence, social and behavioral characteristics, and/or biochemical response appeared to influence patient outcomes.

Route of administration may have a significant effect on patient response. A meta-analysis of 22 acute migraine treatment trials showed greater effect associated with a

Table 1 Placebo response rates from various disease states

Ref.	Medication/ disease state	Therapy received by patient	No. of patients	Responders
[22]	Caffeine	SBP in caffeine	20	13 (65%)
		SBP in placebo	20	7 (35%)
[13]	Hypertension	One of 6 active drugs	1105	643 (58%)
		Placebo	187	58 (30%)
[12]	Analgesia	1st dose naloxone, 2nd placebo	11	2 (18%)
		1st dose placebo, 2nd placebo	14	5 (36%)
[23]	Parkinson's disease	Placebo	198	41 (20.7%) 67 (33.8%) mixed response
[10]	Peptic Ulcer disease	High-dose antacids	19	6 (35%)
		Placebo for high dose	15	2 (13%)
		Low-dose antacid	18	12 (67%)
		Placebo for low dose	17	6 (35%)
[24]	Neuropathic pain	Fentanyl	26	(50%)
		0.9% sodium chloride injection	24	(8.3%)
[25]	Congestive heart failure	Amrinone	47	27 (57.4%)
		Placebo	52	41 (78%)
[26]	Schizophrenia	Fluphenaine deconate	27	2 (7%)
		Placebo	27	8 (30%)

parenteral than an oral route.[15] Of those receiving oral placebo therapy, 25.7% experienced relief compared to 32.4% response in the subcutaneous placebo group.[15] Future trials are necessary to determine the effect of other routes of administration on patient response.

FACTORS AFFECTING PLACEBO RESPONSE

Numerous factors may explain the reason for placebo response and identify patients most likely to respond to placebo. These include preconceived patient views of disease severity, available treatment options, desire of the patient to please the provider, biochemical release, and stress.[16]

Preconceived patient views of illness, presence of an emotional support network, and practitioner response and intervention influence the patient attitude about the disease and its treatment.[16] Patients with acute severe symptoms are more likely to have improvement in symptoms, due to natural or spontaneous recovery, which may be attributed to the placebo. Placebo response in the treatment of acute ulcerative colitis was related to the number of study visits. Greater than three patient visits demonstrated greater placebo response.[11] Response to placebo in individuals suffering from panic disorder was directly related to the severity of the underlying disease. Those with extensive pathologic conditions responded only to active therapy.[17]

Placebo response may be related to the Hawthorne effect.[18] As the practitioner provides more attention to the patient's health, there is often an increased desire of the patient to please the caregiver and to express appreciation for an effective intervention.

Many hypotheses have been proposed about the underlying cause of placebo response such as the release of endogenous endorphins in response to painful stimuli. Patients experiencing postoperative pain after molar extraction responded to placebo due to the release of endorphins.[12]

The percentage of patients responding to placebo increased when stress was associated with pain.[1] Patient anxiety appears to be a factor in determining response to placebo.[18]

On reanalysis of 14 of the 15 clinical trials, the factors accounting for the improvements in the placebo group

included spontaneous improvement, fluctuation of disease symptoms, effects of previous and/or concurrent treatment and medication, conditional switching of placebo treatment, irrelevant response variables, answers given to be polite but not truthful, experimental subordination, conditioned answers, and false assumption of toxic placebo effect.[19] Practitioner and patient expectations directly influence the results and may distort the data.[20] Recall bias, parental assessment, and context influence expectations may affect reporting of subjective outcomes and adverse events.[20] It is difficult to determine the effects related to the treatment versus those related to the supportive, confirming environment.

Placebos have been found to have effects similar to the active medication being compared.[21] Many investigators have attempted to quantify the placebo response. Scales such as the placebo effect scale (PES) and the side effect scale (SES) have been used to identify patients likely to exhibit placebo effects. These scales determine possible predictors of placebo response such as demographic variables, illness characteristics, and diagnostic and symptom variables to identify patients at increased benefit or risk of demonstrating a placebo response.[18] The need for routine use of such scales prior to inclusion in clinical trials and implications of identifying those most susceptible to placebo response require further study.

MISCONCEPTIONS

There are numerous misconceptions or generalizations about placebo response. Common misconceptions include but are not limited to the following: One-third of all patients respond to placebo therapy; response is brief; certain demographic or personality factors predict response; those who respond to placebo therapy do not have medical problems; and giving placebo is equivalent to no intervention.[21] In addition, placebo response in one clinical trial or disease state does not ensure equivalent placebo response in other disease states.[10,12,13,22–26]

USE OF PLACEBOS IN CLINICAL PRACTICE

Placebos employed in the course of general medical practice may be given to patients believed to be experiencing exaggerated symptoms or to those who were unresponsive to current medical therapies. Such patients are likely to receive placebo therapy when practitioners are unable to determine the cause of disease or if inadequate treatment is available.[27,28]

Is it ethical for physicians to prescribe placebos? This question has been debated in the medical literature since the 19th century. Arguments for placebo use have focused on the positive effects noted in clinical trials.[2,10,12,13,22–26]

The primary arguments against placebo use without consent focus on the deception and manipulation involved, and violation of the a priori moral rule that a person deserves respect and should be treated as expected with an active drug.[2] It eliminates the patient's right to make an informed decision about his/her care, diminishes the patient's dignity, and results in decreased trust in the physician/patient relationship. It also advocates the use of medication for every ailment including those without medical justification or for which no treatment is available. Placebo administration may further increase requests for treatment of symptoms, delay appropriate diagnosis and treatment, and result in the withholding of established therapies.

CURRENT DECLARATION OF HELSINKI

The current Declaration of Helsinki was revised in October 2000 to provide guidance to physicians and other medical researchers on the issue of placebo controls when effective agents are available. The changes reflect the ethical concerns raised by the use of placebo controls in pregnant HIV-infected females in Uganda and Thailand. Available agents such as zidovudine have been shown to significantly decrease the incidence of transmission of HIV to the fetus when taken throughout the pregnancy. The revisions stress that the well-being of the human subject takes precedence over the interests of medical progress. Medical research is justified only if the benefits to the patient outweigh the risks and the informed patient consents to participate. The efficacy and safety of the investigational product should be tested against the best current treatment available. If no treatment exists, placebo therapy or no intervention is acceptable. It is important to realize that the Declaration of Helsinki does not have legal power to enforce these changes. These are guidelines for ethical conduct of medical research. Institution-specific IRBs are responsible for enforcing the rules and guidelines for human subject safety and research conduct.

SUMMARY

Placebos are used in clinical practice and research. Placebo response has been demonstrated in a variety of

disease states. Despite the demonstrated efficacy of placebo therapy, the use of placebos in clinical practice may be considered unethical. Attempts by researchers to determine the patient-specific characteristics responsible for placebo response have been unsuccessful. Patient, practitioner, and environmental factors make it difficult to quantify placebo response. The Declaration of Helsinki has been revised to address the issue of placebo use in clinical trials. If an effective agent is available, the new agent should be tested for efficacy against the available effective therapy, not the placebo. Further studies are needed to clearly understand the reasons for placebo response in patients of various demographic characteristics.

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PROFESSIONAL DEVELOPMENT

Poison Information Pharmacy Practice

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INTRODUCTION

Poison information centers, sometimes referred to as poison control centers, provide an important emergency hotline service to the lay public, medical professionals, and individuals from every aspect of society. The primary mission of poison information centers is to provide emergent information about the identification and recognition of actual and potential poisons, the diagnosis of poisoning, and the treatment of poisoning to improve patient care. Most poison information centers provide service 24 hours/day, every day of the year. Pharmacists provide an important function in poison centers by serving as the individuals who respond to poison hot-line emergency calls and by providing overall administrative and clinical management of the poison information center.

EVOLUTION OF POISON INFORMATION CENTERS

In 1950 the American Academy of Pediatrics appointed a committee to explore the problem of accidental injury.[1] The committee disseminated a national survey and the results revealed that a significant percentage of the reported injuries were the consequence of unintentional poisonings. In response to those findings, the Illinois Chapter of the American Academy of Pediatrics, in cooperation with the Illinois Department of Health and seven hospitals, pooled their resources leading to the establishment of the first poison information center (PIC) in Chicago in 1953. The roots of pharmacy in this evolutionary process are quite evident—the director of the first poison center was a pharmacist, Louis Gdalman.[2] The textbooks, scientific literature, and electronic databases of today could only have been dreams of Gdalman and his colleagues as they labored intensively to obtain and compile product ingredient information from manufacturers and to develop basic protocols for the treatment of poisonings.

The first PIC was so successful that other centers evolved and it became apparent quite rapidly that they were replicating the labor-intensive efforts of each other as they compiled product information. Furthermore, they had no way to share the information with each other. In response, the surgeon general instructed the U.S. Public Health Service to develop the National Clearinghouse for Poison Control Centers.[3] The Clearinghouse was charged with tabulating the collective experience of PICs and with providing information on the diagnosis and treatment of poisonings. The first poison information was provided to PICs on cards. Pharmacists served as the primary staff of the National Clearinghouse.

As PICs proliferated the American Association of Poison Control Centers (AAPCC) was founded in 1958.[3] The AAPCC provided an interdisciplinary venue for poison information center staff—that included nurses, pharmacists, physicians, and veterinarians—to gather at an annual scientific meeting and for the eventual development of poison prevention materials and criteria for poison center standardization and regionalization. The American Academy of Clinical Toxicology (AACT) was established in 1968 as the interest in clinical toxicology grew beyond those working in the traditional PIC. Subsequently, as the PIC movement spread, a variety of related international organizations evolved [e.g., Canadian Association of Poison Control Centres (CAPCC), European Association of Poisons Centres and Clinical Toxicologists (EAPCCT), and World Federation of Poison Control Centres (no longer in existence)] that were multidisciplinary in nature.

From the humble beginnings of a single poison center in 1953, the number of centers exploded to 661 by 1978, including over 100 in the state of Illinois alone![1] There were no federal guidelines that regulated the number of or quality of PICs. Some centers operated during daylight hours and not on weekends, others were simply a telephone in an emergency department or pharmacy (answered by the unlucky individual standing closest to the telephone!), and some actually provided 24-hour/day coverage. In about 1980 the AAPCC developed voluntary guidelines to standardize minimal care by certifying qualified centers as Regional Poison Information Centers.

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DOI: 10.1081/E-ECP 120006237

However, the large number of centers flourished until healthcare reform (and associated cost containment) occurred in the late 1980s and 1990s, resulting in significant attrition among poison centers. Today there are only 69 PICs, 54 of which are AAPCC Certified Regional Poison Information Centers.[14]

THE CONTEMPORARY PIC AS A PRACTICE SITE FOR CLINICAL PHARMACISTS

The PIC provides the best career opportunity for the pharmacist who is pursuing an interest in the discipline of clinical toxicology. While there are opportunities to practice clinical toxicology in acute-care settings such the emergency department or critical care unit, the poison center provides a variety of experiences from frontline work as a specialist in poison information to that of a poison center director. To best describe the opportunities for pharmacists, it is important to characterize U.S. poison centers.

Poison Center Certification

There are two types of PICs in the United States—AAPCC Certified Regional Poison Information Centers (RPICs) and nonregional centers. All centers that chose not to participate in the voluntary certification process or fail to become certified are defined as nonregional centers. (See Appendix 1 for the complete description of the AAPCC certification criteria.) In summary, RPICs do the following:

- Provide service 24 hours/day, every day of the year.
- Cover a defined region with a minimum population of 1 million.
- Utilize properly trained nurses or pharmacists to provide telephone consultation.
- Feature administrative/clinical direction by a pharmacist or physician that is board certified in clinical toxicology.
- Feature medical direction by a physician.
- Maintain toxicosurveillance by participating in the AAPCC Toxic Exposure Surveillance System.
- Provide professional and lay education.

Specialists in Poison Information

The typical RPIC responds to approximately 60,000 exposure and information inquiries annually[4] (Fig. 1). Consultations about pharmaceutical agents comprise

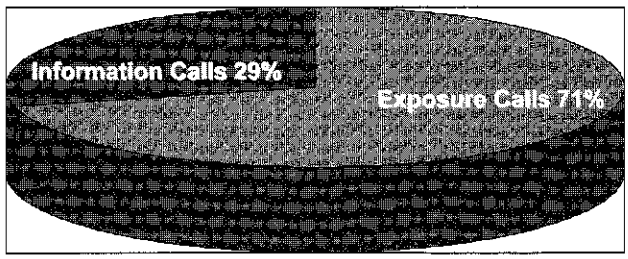

Fig. 1 RPIC call types.

43.1% of PIC calls, cleaning substances 9.9%, personal care products 9.3%, and plants 5.2%.[5] Therefore, the clinical and basic science education of the pharmacist in therapeutics and pathophysiology, pharmacology, pharmacognosy, and chemistry makes them well-suited to serve as a specialist in poison information.

The specialist in poison information (SPI) is the foundation of a PIC. The SPIs respond to incoming poison information calls and document each inquiry on a medical record. Nearly all of the RPICs utilize one of the electronic patient management/medical documentation software programs (e.g., Dotlab, Toxicall). Medical documentation customarily follows the S.O.A.P. approach to medical documentation:

- Subjective complaint.
- Objective findings.
- Assessment.
- Plan.

A variety of sophisticated online databases, such as Poisindex, as well as a multitude of toxicology references and papers from the medical literature, are utilized to provide a toxicology profile of the substance in question and to help the SPI formulate an opinion about the potential morbidity and mortality of an exposure. (Poisindex identifies ingredients for hundreds of thousands of commercial, pharmaceutical, and biological substances. Each substance is linked to one or more management documents providing information on clinical effects, range of toxicity, and treatment protocols for exposures involving the substances.)

Among RPICs there is a pool of 531 SPIs: Pharmacists account for 35% of the SPIs, nurses 58%, and others 7% (Fig. 2).[5] Within nonregional centers there are an additional 58 full-time equivalent pharmacist staff positions. Therefore, it is apparent that there is a career opportunity for pharmacists within this discipline, albeit a somewhat limited one. Nurses dominate RPIC staffing. During the formative years of poison center evolution,

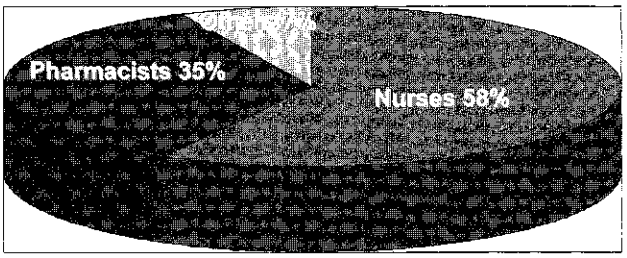

Fig. 2 RPIC staffing.

nurses were utilized more extensively due to their clinical training. However, the clinical training in the pharmacy curriculum and the extensive pharmacology, therapeutics, and chemistry background make the pharmacist well-prepared for a career as a specialist in poison information. Despite these attributes, it is unlikely that pharmacists will erode the current staffing patterns where nurses dominate. The decision to hire nurses instead of pharmacists is based largely on financial motivation, since nursing salaries are generally lower than those of pharmacists. The average RPIC has 7.7–17.0 Certified SPIs on the staff.[4] On an annual basis, the average SPI in an RPIC responds to 3,650 human poisoning exposures or approximately 14 human exposures/8 hour shift.[4] It is important to realize that PICs are open 24 hours/day and that call volume drops dramatically after 11:00 p.m. and does not increase appreciably until approximately 9:00 a.m.[5] (Fig. 3). SPIs working during the peak utilization hours of operation will actually manage 30–45 exposures per 8-hour shift.

Specialists in poison information have the opportunity to become Certified Specialists in Poison Information (CSPI) by qualifying for the AAPCC CSPI Certification Examination (Appendix 2). RPICs must have at least one CSPI on staff at all times. Most RPICs mandate that their SPIs become certified within one to two years of beginning employment at the center. Successful matriculation of the examination is often associated with pay grade enhancement. A CSPI is required to recertify only once every seven years.

Poison Center Director

Each RPIC must have a director who is responsible for the daily administrative and clinical operation of the poison center. Additionally, the RPIC must have a medical director who is responsible for the medical oversight and direction of the center. The majority of RPIC directors are pharmacists (generally Pharm.D.s) and in a limited number of centers a physician fulfills the role of both director and medical director. Pharmacists who aspire to becoming a director of a poison center should consider serving a postgraduate fellowship in an RPIC. Since there are 69 poison centers in the United States, the director position provides a limited but viable and rewarding career opportunity for a pharmacist with postgraduate training in clinical toxicology and poison center management. The AAPCC mandates that nonphysician directors must be eligible for or certified by the American Board of Applied Toxicology (ABAT). The ABAT examination is a rigorous two-day clinical toxicology examination that is administered on an annual basis just prior to the North American Congress of Clinical Toxicology. (See Appendix 3 for more information on the ABAT.)

The Consulting Clinical Toxicologist

The traditional role of the clinical pharmacist in this discipline has been in the PIC as a CSPI or director. A number of pharmacists practice clinical toxicology on a daily basis as part of their clinical pharmacy responsibilities. Clinical pharmacists working in critical care environments such as the emergency department or the critical care unit must have a substantial appreciation of clinical toxicology since unintentional and intentional overdoses are common reasons for hospitalization. There is also a substantial opportunity for the clinical toxicologist to become engaged in consultation with industry through the analysis and interpretation of toxicity issues. The legal arena also provides an opportunity for the clinical toxicologist to serve as an expert witness in the resolution of litigation.

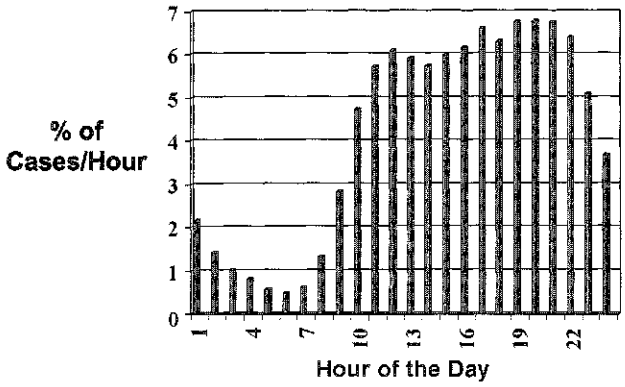

Fig. 3 Poison center call volume by hour.

POISON CENTER AND STAFF COST JUSTIFICATION

There has been significant attrition among poison centers over the last two decades. This is due to the fact that poison centers are generally financial liabilities to their sponsoring institutions and do not generate sufficient revenue to offset operation expenses. This has resulted in the closure of nearly 600 poison centers since 1978. Mistakenly, poison centers have been perceived by the public, medical establishment, and government to be part of the healthcare infrastructure. Each of these entities has had the erroneous perception that one of the others was responsible for funding. This misperception has left many poison centers on the brink of financial disaster. However, poison centers must shoulder some of the blame for this precarious position by failing to diversify poison center revenue sources. The successful poison center should have support from local, regional, and/or state government; from the hospitals that they serve; and from business and industry (serving as a company after-hours medical/poison information service).

Since 1998 there has been intense activity at the federal level to legislate stabilization money from the government and to ensure the future viability of PICs. The Poison Center Enhancement and Awareness Act of 1999 (Appendix 4) will provide funding to: 1) stabilize poison center services, 2) improve access to poison center services by providing a single toll-free number to be shared by all poison centers, 3) provide national poison prevention education, and 4) improve the treatment of poisoning victims. This legislation will fulfill the goals of a recent report by the Department of Health and Human Services, which stated that every United States resident should have access to a certified regional poison center. However, the $20 milion appropriation (reduced from the original $25 million in the Senate and House bills) will not be adequate to totally fund a poison center operation and there will be a continued need to aggressively seek additional funding to support PICs. The clinical pharmacist who chooses a career in a PIC, especially at the director level, must be prepared to identify a variety of financial resources to ensure that the mission of the poison center to improve patient care is not compromised. The influx of federal support will not eliminate the financial scrutiny of poison centers by sponsoring institutions and government. It will be necessary to continuously justify the human and cost-effective benefits of poison centers.[6] The best strategy is to utilize validated facts and data to help strengthen the argument in favor of investing in a PIC.

Financial Benefits

- For each dollar spent on poison center activities, $6.50 is saved.[7]
- When a PIC is utilized by healthcare professionals, the cost per successful outcome is approximately 50% less than that achieved without using a PIC.[8]
- When PICs have closed, admissions secondary to poisoning increased by 16% and outpatient claims increased by 35%.[1]
- Each dollar spent on poison prevention activities saves $3.00.[9]

General Benefits[10]

- Improved healthcare of the poisoned patient.
- Reduction of unintentional poisoning in the home and the workplace.
- Reduction in unnecessary hospital visits and inappropriate use of medical facilities.
- Reduced morbidity by advising callers against the use of antiquated first aid methods and ineffective/dangerous home remedies resources.
- Decreased burden on emergency medical services and emergency transportation.
- Use of toxicosurveillance for the early detection of biochemical terrorism events and hazardous materials leaks/spills.
- Early identification of problems associated with medications and product packaging defects.
- Enhanced patient care through education of the lay public and medical professionals.

INFORMATION RESOURCES

What product does the clinical pharmacist working in a PIC provide? Pharmacist CSPIs provide contemporary information on product toxicity and patient management. Pharmacist clinical toxicologists consult with other healthcare professionals regarding patient diagnosis and management. The poison center product is an intangible entity referred to as *knowledge*. Knowledge is the sum of poison center staff experience and information.

Experience + Information = Knowledge

Toxico-informatics, or converting information to knowledge, is the most formidable challenge that clinical pharmacists in poison centers face in the near future due to the exponential growth of information and technology.[11] For example, available information doubled

between 1750 and 1900—150 years; 1900–1950 saw information double again in only 50 years. From 1960–1992, information doubled at least once every five years. By 2020, it is estimated that information will double every 73 days. Clinical pharmacists working in poison centers must proactively prevent the information explosion from incapacitating centers and must find ways to filter the information to make it usable. Half of knowledge is knowing where to find data and information and then converting them to knowledge once you find them. Twenty-five years ago, pharmacists working in a PIC had a limited number of textbooks, a few hundred papers from the medical literature, and a few pieces of Poisindex microfiche as their information resources. Since that time hundreds of textbooks have been written to address basic clinical toxicology and very specific topics such as botanical toxins. (See Appendix 5 for a list of relevant textbooks.) The advent of the electronic database era has made an incredible number of resources available on general toxicology, hazardous materials, natural toxins, and biochemical terrorism. (See appendix 5 for specific URLs.)

CLINICAL TOXICOLOGY ORGANIZATIONS

Clinical toxicology and poison information are well defined but very small disciplines when compared to mainstream health specialties. Therefore, collaboration among those who practice the specialty is critical.

American Association of Poison Control Centers

For individuals who practice in a PIC it is advisable to become a member of the American Association of Poison Control Centers (AAPCC). The AAPCC is a nationwide organization of poison centers and interested individuals. The main objectives of the AAPCC are: 1) to provide a forum for poison centers and interested individuals to promote the reduction of morbidity and mortality from poisonings through public and professional education and scientific research and 2) to set voluntary standards for poison center operations. The major activities of the AAPCC are:

- Certification of regional poison centers and poison center personnel.
- Interaction with private and government agencies whose activities influence poisoning and poison centers.
- Development of public and professional education programs and materials.
- Collection and analysis of national poisoning data.

For more information or to join the AAPCC contact: AAPCC, 3201 New Mexico Avenue, NW, Suite 310, Washington, DC 20016; Tel.: 202-362-7217, Fax: 202-362-8377, E-mail: aapcc@poison.org, Web site: www.aapcc.org.

American Academy of Clinical Toxicology

Pharmacists who practice in a PIC or in private practice would benefit from membership in the American Academy of Clinical Toxicology (AACT). The AACT was established in 1968 as a not-for-profit multidisciplinary organization uniting scientists and clinicians in the advancement of research, education, prevention, and treatment of diseases caused by chemicals, drugs, and toxins. The founders of the AACT established the Academy to:

- Promote the study of health effects of poisons on humans and animals.
- Unite into one group scientists and clinicians whose research, clinical, and academic experience focus on clinical toxicology.
- Foster a better understanding of the principles and practice of clinical toxicology.
- Encourage development of new therapies and treatment in clinical toxicology.
- Facilitate information exchange among individual members and organizations interested in clinical toxicology.
- Define the position of clinical toxicologists on toxicology-related issues.

Today, the AACT is the largest international clinical toxicology society whose membership is comprised of clinical and research toxicologists, physicians, veterinarians, nurses, pharmacists, analytical chemists, industrial hygienists, poison information center specialists, and allied professionals. The AACT is affiliated with many professional organizations and organizes the North American Congress of Clinical Toxicology and is a cosponsor of the EAPCCT International Congress, which brings clinical toxicologists together annually for scientific meetings. An additional benefit of AACT membership includes the *Journal of Toxicology-Clinical Toxicology* (the official journal of the Academy and the European Association of Poisons Centres and Clinical Toxicologists). The journal is

a leading clinical toxicology journal and has published the AACT/EAPCCT cutting-edge position statements on gastrointestinal decontamination.[12,13] The Academy is also the host organization of the American Board of Applied Toxicology, which certifies nonphysicians as clinical toxicologists—a mandatory certification for PIC directors. The AACT supports career development of members involved in toxicology research through financial awards and sponsorship of fellowships and scholarships. Additionally, the Academy sponsors an electronic bulletin board to foster collaborative clinical toxicology research among its members.

For more information or to join the AACT contact: AACT, 777 East Park Drive, PO Box 8820, Harrisburg, PA 17105-8820; Tel.: 717-558-7750, ext. 1467 Fax: 717-558-7845, E-mail: aact@pamedsoc.org, Web site: www.clintox.org.

European Association of Poisons Centres and Clinical Toxicologists

The European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) was founded in 1964 by a group of physicians and scientists with the specific goal of advancing knowledge and understanding of the diagnosis and treatment of all forms of poisoning. The Association's objectives are to:

- Foster a better understanding of the principles and practice of clinical toxicology in order to prevent poisoning and to promote better care for the poisoned patient, particularly through poison information centers and poison treatment centers.
- Unite into one group individuals whose professional activities are concerned with clinical toxicology whether in a poison center, university, or hospital or in government or industry.
- Encourage research into all aspects of poisoning.
- Facilitate the collection, exchange, and dissemination of relevant information among individual members, poison centers, and organizations interested in clinical toxicology.
- Promote training in, and set standards for the practice of, clinical toxicology and to encourage high professional standards in poison centers and in the management of poisoned patients generally.
- Collaborate with international and integrational organizations including the WHO and European Union.
- Establish and maintain effective collaboration with governments, governmental organizations, professional bodies, and other groups or individuals concerned with clinical toxicology.

For more information or to join the EAPCCT contact: EAPCCT General Secretary, National Poison Information Service, Guy's & St. Thomas Hospital Trust, Medical Toxicology Unit, Avonley Road, London SE14 5ER, U.K.; Tel.: 44-207-771-5310, Fax: 44-207-771-5309, E-mail: alex.campbell@gstt.sthames.nhs.uk, Web site: www. eapcct.org.

Active participation in these societies and their annual meetings provides an excellent venue to learn about contemporary issues in clinical toxicology and poison information practice. All of the societies are interdisciplinary and cater to the needs of people with an interest in clinical toxicology irrespective of the individual's health science training. Membership in one or all of the societies provides the best opportunity to network with clinical toxicologists.

THE NATION'S CERTIFIED REGIONAL POISON INFORMATION CENTERS

There are 54 RPICs serving the majority of the United States. Clinical pharmacists who are looking for a career opportunity in poison information practice should contact those centers for additional information. (A current list of all PICs in the United States may be found at www. aapcc.org.)

APPENDIX 1: AAPCC REGIONAL POISON INFORMATION CENTER CERTIFICATION CRITERIA

Introduction

The purpose of this document is to establish criteria by which poison centers and poison center systems can be recognized as possessing the qualifications needed to adequately serve their designated population.

Definitions

A *poison center* is an organization that provides the following services to a region which it has been designated to serve: 1) poison information, telephone management advice, and consultation about toxic exposures; 2) hazard surveillance to achieve hazard elimination; and 3) professional and public education in poison prevention, diagnosis, and treatment.

A *poison center system* consists of two or more poison centers functionally and electronically linked to provide poison center services.

A *certified poison center system* consists of a poison center system which either: 1) collectively meets the same criteria as a single certified poison center, or 2) consists of a number of centers serving a given region, all of which are certified individually. There cannot be any state-designated noncertified centers in the region of a certified system unless they are components of the system.

I. Determination of Region

A. Geographical characteristics

A certified poison center or system may serve a single state, a multistate area, or only a portion of a state. The region should be determined by state authorities in conjunction with local health agencies and healthcare providers. In instances where multiple states are involved, designation from each state is necessary. Documentation of state designations of poison centers and systems must be in writing and must clearly delineate the region to be served, the services to be provided, and the exclusivity of the designation. In instances where a state declines in writing to designate any poison center or system, designation by other political or health jurisdictions (e.g., county, health district) may be an acceptable alternative. In instances where more than one center or system is designated to serve the same area, evidence of cooperative arrangements must be provided.

B. Population base

The certified poison center or poison center system must provide evidence that it adequately serves its entire region. It is unlikely that a single poison center could adequately serve more than 10 million people.

C. Penetrance

The *penetrance* of a poison center or system in a region is defined as the number of human poison exposure cases handled per 1000 population per year. Penetrance is assumed to be most affected by the public's awareness of the appropriate use of the poison center. A certified poison center or system must demonstrate a minimum average penetrance of 7.0 throughout its service area. Poison centers and poison center systems should strive to achieve a penetrance of 12 to 15 throughout the region served, by increasing or maintaining awareness of poison center services.

II. Regional Poison Information Service

A. The certified poison center or system shall provide information 24 hours/day, 365 days/year to both health professionals and the public

This criterion will be considered to be met if the certified poison center has at least one Specialist in Poison Information in each center at all times, sufficient additional staff to promptly handle each center's incoming calls, and the availability of the medical director or qualified designee, on-call by telephone, at all times.

Only if Part of a System. Certified poison centers may divert calls to another certified poison center within the same state, within a contiguous region, or to the closest certified poison center, if: 1) unequivocal continuity of clinical care is achieved through functional access to all open patient records, and 2) the receiving certified poison center staff are fully trained and informed about all healthcare, EMS, and lab facility capabilities and regional toxicology variations. (The criteria relating to diversion of calls, functional access to open patient records, and knowledge of facilities and regional toxicology variations do not apply when assisting another poison center in a disaster situation.)

B. The certified poison center or system shall be readily accessible by telephone from all areas within the region

1. The certified poison center or system must maintain a direct incoming telephone system that is extensively publicized throughout the region to both health professionals and the public.
2. The certified poison center or system must maintain a telecommunications system adequate to assure ready access and must provide data verifying ready access.
3. In the absence of a toll-free system, the certified poison center or system must demonstrate that the lack of a toll-free service is not an impediment to public use of the center.
4. A certified poison center or system may not impose a direct fee to individual members of the lay public (either by direct billing or pay-for-call services) for poison exposure emergency calls received from the public within its region.
5. The certified poison center or system must be able to respond to inquiries in languages other than English as appropriate to the region using language translation services, interpreters, and/or bilingual staff.

6. Access for hearing-impaired individuals must be provided.
7. A plan to provide poison center services in response to natural and technological disasters must be in place.

C. The certified poison center or system shall maintain comprehensive poison information resources (at each site)

This criterion will be considered to be met if each center maintains:

1. One or more comprehensive product information resources, immediately available to the Specialist in Poison Information at all times.
2. Current comprehensive references covering both general and specific aspects of acute and chronic poisoning management immediately available to the Specialist in Poison Information at all times. There must be access to the most current primary information resources and ready availability of a major medical library or comparable online resources.
3. Evidence of the competency of all specialists and information providers in using texts, information resources, and primary literature.

D. The certified poison center or system shall maintain written operational guidelines which provide a consistent approach to evaluation and management of toxic exposures

This criterion will be considered to be met if the certified poison center or system provides written operational guidelines which include but are not limited to the follow-up of all potentially toxic exposures and appropriate criteria for patient disposition. These guidelines must be available in the center at all times and must be approved in writing by the medical director of the program. In addition, these guidelines must have evidence of periodic review, and the center must provide evidence of action taken to remedy problems with guideline content or guideline adherence through quality assurance programs and staff education.

E. Staffing requirements and qualifications for the certified poison center or system

1. Toxicological Supervision. Certified poison centers and each center within a certified poison center system must provide full-time toxicological supervision. This must include at least one full-time equivalent of on-site toxicological supervision and appropriate backup. These components must meet the specific criteria listed below. Each site of a certified poison center system must meet the requirements for medical and managing direction.

A) Medical direction and medical backup.

1) Medical direction may be provided by a single medical director or by more than one individual. If more than one individual provides medical direction, one individual must be designated as medical director and that person is responsible for approving other individuals involved and for coordinating their activities.
2) The medical director and all other individuals designated as providers of medical direction must be board-certified in medical toxicology or board-prepared in medical toxicology as determined by a letter from the board indicating that the candidate will be allowed to sit for the next examination. Such board-prepared physicians must successfully complete the examination within two consecutive administrations of the exam. Board certification through either the American Board of Medical Toxicology (pre-1994) or through the American Board of Medical Specialties subspecialty exam in medical toxicology (after 1994) is acceptable.
   Physicians without board certification in medical toxicology will be considered qualified as medical directors for the purpose of determining compliance with the current criteria if: 1) the physician served as medical director of a poison center certified by AAPCC as of September 14, 1998; and 2) the physician met the immediately previous AAPCC criteria for medical directors on September 14, 1998.
3) The medical director and all other individuals designated as providers of medical direction must have medical staff appointments at an inpatient treatment facility, must be involved in the management of poisoned patients, and must regularly consult with Specialists in Poison Information about the management of poisoned patients.
4) The individual or individuals providing medical direction must individually or collectively devote at least 20 hours per week of professional activity time to toxicology. An additional 10 hours per week of medical direction time must be provided for each 25,000 human poison exposure cases per year received by the certified poison center, above

Table 1 Time requirements for medical directions

No. of human poison exposures	100% PC hours	Total tox hours
25,000	10	20
50,000	20	30
75,000	30	40
100,000	40	50
125,000	50	60

the initial 25,000 human poison exposure cases. Time applied to this total should conform to the following standards:

a. Up to 10 hours per week of the total time applied to medical direction may consist of toxicology activities not directly related to certified poison center operation, such as clinical, academic, teaching, and research activities. No more than 10 percent of clinical time in emergency department, clinic, ward, or intensive care unit service will apply to this total, unless specific documentation is provided to verify that the additional time was directly related to toxicology.

b. The remainder of the total time applied to medical direction activities must consist of poison center operational activities during the time that is 100 percent dedicated to on-site medical direction at each certified poison center or site of a poison center system.

The time requirements for medical direction are summarized in Table 1.

5) Medical backup must be available, in a timely manner, at all times. If not provided by the medical director, medical backup may be provided by those providing medical direction or other individuals designated by the medical director. All medical backup must be provided by board-certified or board-prepared medical toxicologists. Other individuals identified and qualified by the medical director (e.g., fellows, managing director) may serve as immediate certified poison center backup if timely secondary backup is provided at all times by a board-certified or board-prepared medical toxicologist. Direct clinical effort as backup can be applied to item 4.A. above.

B) Managing direction.

1) The managing director provides direct toxicological supervision of poison center staff, strategic planning, and oversight of administrative functions of programs, e.g., staff training, quality assurance, budgeting.

2) Managing direction may be provided by a single managing director or may be provided by more than one individual, each with the qualifications identified below. If more than one individual is involved in providing managing direction, one individual must be designated as managing director (or comparable title), and that person is responsible for coordinating managing direction activities.

3) The managing director must be a nurse with a baccalaureate degree, associate degree, or three-year diploma; a pharmacist; or a physician or may hold a degree in a life science discipline if a diplomate of the American Board of Applied Toxicology. If the managing director is also the medical director, this person must have a full-time commitment to the poison center.

4) The managing director with toxicological supervision responsibilities must be board-certified or board-prepared, as evidenced by a letter from the appropriate board indicating that the candidate will be allowed to sit for the next examination. For physicians this board can be the ABMT (pre-1994) or the ABMS subspecialty examination in medical toxicology (post-1994). For all others, the board must be the American Board of Applied Toxicology. Candidates for the board examination must successfully complete the examination within two consecutive administrations of the examination. Individuals without board certification in applied toxicology will be considered qualified as managing directors for the purpose of determining compliance with the current criteria if: 1) the individual served as managing director of a poison center certified by AAPCC as of September 14, 1998; and 2) the individual met the immediately previous AAPCC criteria for managing directors on September 14, 1998.

2. Specialists in Poison Information. A Specialist in Poison Information must be on duty in the certified poison center, or at each functioning site of a poison center system, at all times.

A) Specialists in Poison Information must be: 1) a nurse with a baccalaureate degree, associate degree, or three-year diploma; a pharmacist; or a physician; 2) currently certified by AAPCC as a Specialist in Poison Information; 3) a diplomate of the American Board of Applied Toxicology; or

4) a board-certified medical toxicologist. Specialists in Poison Information must be qualified to understand and interpret standard poison information resources and to transmit that information in a logical, concise, and understandable way to both health professionals and the public.

B) All Specialists in Poison Information must complete a training program approved by the medical director and, unless a diplomate of the American Board of Applied Toxicology or a board-certified medical toxicologist, must be certified by AAPCC as a Specialist in Poison Information within two examination administrations of his or her initial eligibility for certification. If a Specialist in Poison Information fails to pass a certification exam within two exam administrations of his or her initial eligibility for certification, he or she may work only as a Poison Information Provider under direction as described in Section II.E.3. If an individual fails a recertification examination or does not take a recertification examination, that person reverts to the position of Specialist in Poison Information.

C) Specialists in Poison Information not currently certified by AAPCC as Specialists in Poison Information must spend an annual average of no fewer than 16 hours per week in poison center–related activities, including providing telephone consultation, teaching, public education, or in poison center operations. Specialists in Poison Information currently certified by AAPCC as Specialists in Poison Information must spend an annual average of no fewer than 8 hours per week in poison center–related activities, including providing telephone consultation, teaching, public education, or in poison center operations. Individuals who do not meet this criterion may work as Poison Information Providers with direction as described in II.E.3.

D) All Specialists in Poison Information, whether full-time or part-time, must be 100% dedicated to poison center activities during periods when they are assigned to the center. Poison center calls must be their first priority. In cases where a poison center assumes other roles, the center must demonstrate policies and safeguards that assure that poison center calls are given priority and that these other activities pose no conflict with poison exposure cases and cause no reduction of service quality or quantity within the certified poison center's region.

E) At the time of initial application for poison center certification and thereafter, at least 50% of Specialist in Poison Information full-time equivalent positions (FTEs) must be filled by Certified Specialists in Poison Information. For certified poison center systems, at least 50% of Specialists in Poison Information FTEs at each site must be Certified Specialists in Poison Information.

F) To maintain experience and expertise, on average each certified poison center must handle at least 2,000 human poison exposures per SPI/PIP full-time equivalent.

3. Other Poison Information Providers. Other poison information providers must be qualified to understand and interpret standard poison information resources and to transmit that information understandably to both health professionals and the public. This requirement will be considered to be met if the person has an appropriate health-oriented background and has specific training and/or experience in poison information sciences. While providers may be part-time staff or have a part-time commitment to the poison center, 100% of their time should be dedicated to poison center activities while assigned to the center. At all times, poison information providers must be under the on-site direction of a Certified Specialist in Poison Information, a qualified managing director, or the medical director; these individuals may provide direction for no more than two poison information providers at one time.

4. Certified Poison Center Specialty Consultants. Certified poison center specialty consultants should be qualified by training or experience to provide sophisticated toxicology or patient care information in their area(s) of expertise. These consultants should be available on-call and provide consultation on-call on an as-needed basis. The list of consultants should reflect the type of poisonings encountered in the region.

5. Administrative Staff. Certified poison center administrative personnel should be qualified by training and/or experience to supervise finances, operations, personnel, data analysis, and other administrative functions of the certified poison center.

6. Education Staff.

A) Professional education. Professional education personnel should be qualified by training or experience to provide quality professional education lectures or materials to health professionals. This role will be supervised by the medical director.

B) Public education. Public education personnel should have proven skills in communication and program plan-

ning, implementation, and evaluation, and/or an appropriate educational background with which to provide public-oriented presentations about poison center awareness and the value of the poison center, poison prevention, and first aid for poisoning. This role will be supervised by the medical and/or managing director.

F. The certified poison center or system shall have an ongoing quality improvement program

1. A certified poison center or system shall implement quality assurance activities which incorporate specific monitoring parameters and staff education programs.
2. A certified poison center or system shall demonstrate that patient outcomes are monitored regarding high-risk, high-volume, or problem-prone cases. The corrective actions taken to improve patient care shall be documented. In addition, the certified poison center should demonstrate monitoring of customer satisfaction and assessment of staff competency.

III. Regional Treatment Capabilities

The certified poison center or system shall identify the treatment capabilities of the treatment facilities of the region

At a minimum, the certified poison center or system should: 1) identify emergency and critical care treatment capabilities within the region for adults and children; 2) have a working relationship with all poison treatment facilities in its region; 3) understand the analytical toxicology facilities in the region and how to interface with them; 4) understand how the region's prehospital transportation system is structured and how to interface with it; and 5) know where critical antidotes are available within the region and how they can be transferred between facilities when necessary.

IV. Data Collection System

A. The certified poison center or system shall keep records of all cases handled by the center in a form that is acceptable as a medical record. This criterion will be considered to be met if the Center completes a record that contains data elements and sufficient narrative to allow for peer review and medical and/or legal audit, and such records are retrievable.

B. The certified poison center or system must submit all its human exposure data (except as noted in IV.B.1.) to AAPCC's Toxic Exposure Surveillance System meeting specified submission deadlines and quality requirements and including all required data elements.
   1. The submission of human exposure data derived from industry contracts is encouraged but not required for certification.
   2. Certified poison centers that withhold industry-derived human exposure data must annually submit the number of industry-derived human exposures that were withheld.

C. The certified poison center or system shall tabulate its experience for regional program evaluation and hazard surveillance on at least an annual basis. This criterion will be considered to be met if the center completes an annual report summarizing its own experience.

D. The certified poison center shall monitor the emergence of poisoning hazards and take specific actions to eliminate poisoning hazards.

V. Professional and Public Education Programs

A. The certified poison center or system shall provide information on the management of poisoning to the health professionals throughout the region who care for poisoned patients. This criterion will be considered to be met if the certified poison center offers ongoing information about poison center access and services and updates on new and important advances in poisoning management to the health professionals throughout the region.

B. The certified poison center or system shall provide a variety of public education activities targeting identified at-risk populations. The programs shall address poisoning dangers, poison prevention strategies, first aid for poisoning, and when and how to access poison center services. These programs must be implemented throughout the certified poison center's region.

VI. Association Membership

The applicant poison center and each site in a poison center system must be an institutional member in good standing of the American Association of Poison Control Centers. (Approved April 1988 by the AAPCC Board of Directors. Amended October 1991; September 1992; January 1996; September 14, 1998.)

APPENDIX 2: CERTIFICATION EXAMINATION FOR SPECIALISTS IN POISON INFORMATION

The AAPCC Certification Examination for Specialists in Poison Information is intended for poison center staff whose primary job is handling calls involving human toxic exposures. The exam is administered annually at 40–50 test sites throughout the United States. and Canada. The exam takes place each year in the afternoon of the *second Wednesday in May*. Successful completion of this examination will lead to the designation of Certified Specialist in Poison Information. To maintain certification, the examination must be passed every *seven years*. Applicants must meet the following criteria to sit for the examination:

- Applicants must be members of the AAPCC. This criterion will be considered to be met by either individual membership or by employment at a poison center which is an institutional member.
- Candidates for certification must be registered nurses, pharmacists, physicians, or previously certified specialists in poison information. Physicians are eligible only if they are primarily employed as specialists in poison information, meet the criteria of one year experience, and have handled at least 2,000 human poison exposure telephone consultations. It is intended that physicians take other qualifying exams such as that given by the American Board of Medical Toxicology instead. Center directors, medical directors, assistant directors, consultants, and toxicology fellows in training may *not* apply for certification.
- The candidate must be currently employed as a specialist in poison information. The specialist in poison information must have at least one year (2000 hours) of experience providing telephone poison center consultations and have handled an accumulated 2000 cases. The recommendation of the director of the poison center is required to be eligible to sit for the exam.
- Part-time information specialists must be able to demonstrate at least 2000 hours' experience providing poison center consultations. (For example, a staff member working half-time must work for two years to meet the equivalent part-time experience clause.) Staff of poison centers with personnel performing other duties besides poison control (nursing, pharmacy staffing) may be eligible for the Certification Examination if they can demonstrate unequivocally that they have handled at least 2000 human poison exposure calls, and spent at least 2000 hours providing poison center consultations.

Appropriate documentation will require either:

- Copies of annual call volume statistics for the center listed by human exposures, inquiries, and staff member receiving call, or
- Documentation of percent effort dedicated to poison center operation, primary department, number of hours worked in that department each week, duration of employment (in weeks), and annual call volume for the center. This documentation must be verified and signed by the poison center director. Any figures which clearly demonstrate 2000 hours of experience handling telephone poisoning consultations and sufficient time expended (based on the center's call volume) to have handled at least 2000 calls will be accepted.

Application forms are mailed to poison center directors in February. Application forms must be received by AAPCC by the stated deadline. Applications will be accepted only if:

- All items are completed.
- An application fee is enclosed.
- A photocopy of the applicant's nursing, pharmacy, or medical license; diploma or certificate; or CSPI certificate is also enclosed.
- Applications are received by the announced deadline.

Applicants should not apply if they do not meet these criteria. Application fees for unqualified applicants will not be refunded. Partial refunds will be made to qualified applicants who are unable to sit for the examination if the AAPCC office is notified no later than 2 weeks prior to the examination date.

Currently certified specialists in poison information are not required to be recertified until seven years from the time of certification. If a certified specialist seeks to be recertified before the seven years have elapsed, he/she must pass the examination in order to maintain certification.

APPENDIX 3: THE AMERICAN BOARD OF APPLIED TOXICOLOGY (ABAT)

The American Academy of Clinical Toxicology established the American Board of Applied Toxicology (ABAT) to provide special recognition to practitioners of clinical toxicology who demonstrate exceptional knowledge, experience, and competence. ABAT exists as a self-governing entity whose membership consists solely of all current diplomates of the ABAT. ABAT is

governed by a board of directors elected by ABAT membership from among its diplomates.

All ABAT functions are undertaken in accordance with ABAT bylaws and the bylaws of AACT; these bylaws and all regulations and procedures are promulgated by ABAT. ABAT is a not-for-profit organization. No member of ABAT receives or derives any profit from the operation of ABAT and no part of the net income of ABAT benefits any individual member. ABAT is not involved in authorizing or designating any political lobby action. The principal office of ABAT is usually established in the city of the residence of the president.

Purpose of ABAT

ABAT was created as a not-for-profit organization for the unique purpose of fostering the development of clinical toxicology among the nonphysician, nonveterinarian members of the American Academy of Clinical Toxicology by:

- Advancing the science, study, and practice of clinical toxicology.
- Improving the quality of clinical toxicology consultation available to the public.
- Establishing and maintaining standards of excellence for nonphysician practitioners by developing and administering examinations, as well as other criteria, for the certification and recertification of these practitioners in clinical toxicology.
- Granting certificates and other forms of recognition to professionals who demonstrate exceptional ability in clinical toxicology.
- Maintaining a registry of ABAT diplomates and, upon request, furnishing lists of ABAT diplomates to the public, governmental agencies, healthcare professionals, and educational institutions.

ABAT Certification Examination Credentialling Information

Applicants must meet the following initial criteria to become a candidate for examination:

1. Applicants must be a graduate of a college or university with an earned doctoral degree in a biomedical discipline. Applicants without doctoral degrees must possess a baccalaureate degree in a health science discipline, such as pharmacy or nursing, followed by a minimum of five years of full-time professional experience in applied clinical toxicology. Scholastic course work is not considered to be professional experience.

   Because the American College of Medical Toxicology and the American Board of Veterinary Toxicology are responsible for certification in their respective areas, applicants holding the Doctor of Medicine, Doctor of Osteopathy, or Doctor of Veterinary Medicine degree are *not eligible* to sit for the ABAT examination.

2. Applicants must complete at least 12 months of postdoctoral training (i.e., residency or fellowship) in clinical toxicology or a closely related field. Applicants without postdoctoral training must have a minimum of at least three years of professional experience related to applied clinical toxicology after completion of their doctoral degree. To be prepared for the examination, candidates should have considerable clinical experience and an understanding of the clinical and environmental factors associated with various types of toxicological problems. Examples of activities related to the practice of applied clinical toxicology include consulting with medical personnel on patient care issues; having administrative responsibility for a poison control center with consultative responsibilities; rendering opinions on product toxicity; teaching clinical toxicology to students, practitioners, or colleagues; collaborating with medical toxicologists; and conducting research in applied clinical toxicology.
3. Applicants must demonstrate experience in all the areas of clinical, research, and teaching activities and leadership. An abundance of experience in one area will not substitute for lack of experience in another.
4. Applicants holding a degree in a healthcare profession in which licensing is required must be in good standing with the appropriate jurisdictional board and must be eligible for, or possess, a valid, unrestricted license to practice. A copy of the license must accompany the application.
5. Applicants must be members in good standing of the American Academy of Clinical Toxicology at the time of their application.

Credentialling Committee Review

Following receipt of the completed application and application fee, the candidate's submission is reviewed by the Credentialling Committee. The committee uses a standardized credential review document among the application reviewers. A formal letter from the president

of ABAT will inform the candidate of the committee's decision, and if required, will list areas of improvement the committee felt would allow the candidate to successfully pass credential review on a subsequent submission. Once credentialled, an applicant must take the exam within two examination cycles.

Application Fees

A combined application and testing fee of $400, made payable to the American Board of Applied Toxicology, must accompany the application. If credentialling is denied for any reason, the $300 portion for the examination will be refunded.

APPENDIX 4: S.632 POISON CONTROL CENTER ENHANCEMENT AND AWARENESS ACT

One Hundred Sixth Congress of the United States of America

At the second session

Begun and held at the City of Washington on Monday, the twenty-fourth day of January, two thousand

An Act

To provide assistance for poison prevention and to stabilize the funding of regional poison control centers.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Sec. 1. Short Title

This Act may be cited as the 'Poison Control Center Enhancement and Awareness Act.'

Sec. 2. Findings

Congress makes the following findings:

(1) Each year more than 2,000,000 poisonings are reported to poison control centers throughout the United States. More than 90 percent of these poisonings happen in the home. Fifty-three percent of poisoning victims are children younger than 6 years of age.

(2) Poison control centers are a valuable national resource that provide lifesaving and cost-effective public health services. For every dollar spent on poison control centers, $7 in medical costs are saved. The average cost of a poisoning exposure call is $32, while the average cost if other parts of the medical system are involved is $932. Over the last 2 decades, the instability and lack of funding has resulted in a steady decline in the number of poison control centers in the United States. Within just the last year, 2 poison control centers have been forced to close because of funding problems. A third poison control center is scheduled to close in April 1999. Currently, there are 73 such centers.

(3) Stabilizing the funding structure and increasing accessibility to poison control centers will increase the number of United States residents who have access to a certified poison control center, and reduce the inappropriate use of emergency medical services and other more costly healthcare services.

Sec. 3. Definition

In this Act, the term 'Secretary' means the Secretary of Health and Human Services.

Sec. 4. Establishment of a National Toll-Free Number

(a) IN GENERAL—The Secretary shall provide coordination and assistance to regional poison control centers for the establishment of a nationwide toll-free phone number to be used to access such centers.

(b) RULE OF CONSTRUCTION—Nothing in this section shall be construed as prohibiting the establishment or continued operation of any privately funded nationwide toll-free phone number used to provide advice and other assistance for poisonings or accidental exposures.

(c) AUTHORIZATION OF APPROPRIATIONS—There is authorized to be appropriated to carry out this section, $2,000,000 for each of the fiscal years 2000 through 2004. Funds appropriated under this subsection shall not be used to fund any toll-free phone number described in subsection (b).

Sec. 5. Establishment of Nationwide Media Campaign

(a) IN GENERAL—The Secretary shall establish a national media campaign to educate the public and

healthcare providers about poison prevention and the availability of poison control resources in local communities and to conduct advertising campaigns concerning the nationwide toll-free number established under Section 4.

(b) CONTRACT WITH ENTITY—The Secretary may carry out subsection (a) by entering into contracts with 1 or more nationally recognized media firms for the development and distribution of monthly television, radio, and newspaper public service announcements.

(c) AUTHORIZATION OF APPROPRIATIONS—There is authorized to be appropriated to carry out this section, $600,000 for each of the fiscal years 2000 through 2004.

Sec. 6. Establishment of a Grant Program

(a) REGIONAL POISON CONTROL CENTERS—The Secretary shall award grants to certified regional poison control centers for the purposes of achieving the financial stability of such centers, and for preventing and providing treatment recommendations for poisonings.

(b) OTHER IMPROVEMENTS—The Secretary shall also use amounts received under this section to—

(1) Develop standard education programs;
(2) Develop standard patient management protocols for commonly encountered toxic exposures;
(3) Improve and expand the poison control data collection systems;
(4) Improve national toxic exposure surveillance; and
(5) Expand the physician/medical toxicologist supervision of poison control centers.

(c) CERTIFICATION—Except as provided in subsection (d), the Secretary may make a grant to a center under subsection (a) only if—

(1) The center has been certified by a professional organization in the field of poison control, and the Secretary has approved the organization as having in effect standards for certification that reasonably provide for the protection of the public health with respect to poisoning; or
(2) The center has been certified by a State government, and the Secretary has approved the State government as having in effect standards for certification that reasonably provide for the protection of the public health with respect to poisoning.

(d) WAIVER OF CERTIFICATION REQUIREMENTS—

(1) IN GENERAL—The Secretary may grant a waiver of the certification requirement of subsection (c) with respect to a noncertified poison control center or a newly established center that applies for a grant under this section if such center can reasonably demonstrate that the center will obtain such a certification within a reasonable period of time as determined appropriate by the Secretary.
(2) RENEWAL—The Secretary may only renew a waiver under paragraph (1) for a period of 3 years.

(e) SUPPLEMENT NOT SUPPLANT—Amounts made available to a poison control center under this section shall be used to supplement and not supplant other Federal, State, or local funds provided for such center.

(f) MAINTENANCE OF EFFORT—A poison control center, in utilizing the proceeds of a grant under this section, shall maintain the expenditures of the center for activities of the center at a level that is not less than the level of such expenditures maintained by the center for the fiscal year preceding the fiscal year for which the grant is received.

(g) MATCHING REQUIREMENT—The Secretary may impose a matching requirement with respect to amounts provided under a grant under this section if the Secretary determines appropriate.

(h) AUTHORIZATION OF APPROPRIATIONS—There is authorized to be appropriated to carry out this section, $25,000,000 for each of the fiscal years 2000 through 2004.

APPENDIX 5: MICROMEDEX ELECTRONIC DATABASES

CHRIS: U.S. Coast Guard chemical hazard response information.

Dolphin Software: Over 160,000 material safety data sheets.

Drugdex: Extensive pharmaceutical information.

Drug-Reax: Drug interaction information on over 8000 pharmaceuticals.

Fisher Scientific/ACROS Organics MSDS: Over 18,000 material safety data sheets for pure chemicals. Available in 5 different languages.

Hazardtext: Emergency response information for hazardous material emergencies.

HDSB from NLM: Health and environmental effects of over 4500 toxic chemicals.

Identidex: Tablet and capsule identification system.

Index Nominum: International drug directory.

Infotext: Environmental health and safety information directed toward occupational hygienists.

IRIS: U.S. Environmental Protection Agency health risk assessment information for over 450 chemicals.

LOLI: Environmental, international, and state regulations on chemicals maintained by ChemAdvisor.

NAERG: 1996 North American Emergency Response Handbook.

NIOSH Pocket Guide: Occupational information including exposure limits, incompatibilities, and reactivities.

NJ Hazardous Substances Fact Sheets: Employee-oriented information on 700 hazardous substances developed by the New Jersey Health Department.

OHM/TADS: Physiochemical and toxicological information on 1400 substances. Includes oils and other environmental hazards.

Poisindex: Ingredient and clinical toxicology management information on over 1 million substances.

RegsLink: Access to federal and state chemical regulatory information.

Reprorisk: Contains 4 databases on reproductive risk information.

RTECS from NIOSH: Registry of the toxic effects of over 142,000 substances.

Safetydex: Over 8000 hospital-specific material safety data sheets.

Tomes: Medical and hazard information for chemicals.

APPENDIX 6: STANDARD TOXICOLOGY TEXTBOOKS

General Toxicology

- *Poisoning and Toxicology Compendium with Symptoms Index*, Jerrold B. Leikin, and Frank P. Paloucek; Lexi-Comp, Hudson, Ohio, 1998.
- *Clinical Management of Poisoning and Drug Overdose*, Third Edition; Lester M. Haddad, Michael W. Shannon, and James F. Winchester; WB Saunders, Philadelphia, Pennsylvania, 1998.
- *Goldfrank's Toxicologic Emergencies*, Sixth Edition; Lewis R. Goldfrank, Neal E. Flomenbaum, Neal A. Lewin, Richard S. Weisman, Mary Ann Howland, and Robert S. Hoffman; Appleton and Lange, Stamford, Connecticut, 1998.
- *Toxicology of the Eye*, Fourth Edition; W. Morton Grant, and Joel S. Schuman; Charles C Thomas, Springfield, Illinois, 1993.
- *Casarett and Doull's Toxicology*, Sixth Edition; Curtis D. Klaassen; McGraw-Hill, New York, New York, 2001.

Hazardous Materials Toxicology

Hazardous Materials Toxicology: Clinical Principles of Environmental Health, Second Edition; John B. Sullivan, Jr. and Gary R. Krieger; Williams and Wilkins, Baltimore, Maryland, 2001.

Sax's Dangerous Properties of Industrial Materials, Eighth Edition; Richard J. Lewis, Sr.; Van Nostrand Reinhold, New York, New York, 1992.

Occupational, Industrial, and Environmental Toxicology; Michael I. Greenberg, Richard J. Hamilton, and Scott D. Phillips; Mosby, St. Louis, Missouri, 1997.

Proctor and Hughes' Chemical Hazards of the Workplace, Fourth Edition; Gloria J. Hathaway, Nick H. Proctor, James P. Hughes, and Michael L. Fischman; Van Nostrand Reinhold, New York, New York, 1996.

Plants and Mushrooms

Handbook of Mushroom Poisoning: Diagnosis and Treatment; David G. Spoerke and Barry H. Rumack; CRC Press, Boca Raton, Florida, 1994.

AMA Handbook of Poisonous and Injurious Plants; Kenneth F. Lampe and Mary Ann McCann; American Medical Association, Chicago, Illinois, 1985.

Fetal Risk and Human Lactation

Breastfeeding: A Guide for the Medical Profession, Fifth Edition; Ruth A. Lawrence and Robert M. Lawrence; Mosby, St. Louis, Missouri, 1999.

A Reference Guide to Fetal and Neonatal Risk Drugs in Pregnancy and Lactation, Fourth Edition; Georald G. Briggs, Roger K. Freeman, and Sumner J. Yaffe; Williams and Wilkins, Baltimore, Maryland, 1994.

Herpatology

Snake Venom Poisoning, Second Edition; Findlay E. Russell; Scholium International, Great Neck, New York, 1983.

Alternative Medicines

Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on a Scientific Basis; Norman Grainger Bisset; Medpharm, Stuttgart, Germany, 1989.

The Lawrence Review of Natural Products; Facts and Comparisons; Facts and Comparisons, St. Louis, Missouri, 1999.

Analytical Toxicology

Disposition of Toxic Drugs and Chemicals in Man, Fourth Edition; Randall C. Baselt and Robert H. Cravey; Chemical Toxicology Institute, Foster City, California, 1995.

Bio-chemical Terrorism

Textbook of Military Medicine Part I—Medical Aspects of Chemical and Biological Warfare; Russ Zajtchuk, Editor; Department of the Army, Bethesda, Maryland, 1997.

Chemical Warfare Agents; Timothy C. Marrs, Robert L. Maynard and Frederick R. Sidell; John Wiley and Sons, New York, New York, 2000.

Handbook of Chemical and Biological Warfare Agents; D. Hank Ellison; CRC Press, Boca Raton, Florida, 2000.

Military Chemical and Biological Agents; James A.F. Compton; Telford Press, Caldwell, New Jersey, 1987.

Chemical Warfare Agents; Satu M. Somani; Academic Press, San Diego, California, 1992.

APPENDIX 7

General Toxicology Searching

General Medical and Clinical Toxicology Guide to the Internet
http://www.swmed.edu/toxicology/toxlinks.html
This site provides a single access point to numerous PIC Web sites, journals that publish clinical toxicology papers, and other links to important clinical toxicology information.

MedLine—PubMed
http://www.ncbi.nlm.nih.gov/pubmed/
This site provides online MedLine searching capabilities.

National Academy Press
http://www.nap.edu/catalog/6035.html
Catalog site for publications from the National Academy of Sciences.

National Library of Medicine
http://www.nlm.nih.gov
Entry point for the National Library of Medicine including general information, databases, and photographic archives.

National Library of Medicine's Search Site via Internet Grateful Med
http://igm.nlm.nih.gov/
The Internet Grateful Med Web site provides a variety of database accesses to a variety of searches including MEDLINE, AIDS line, AIDS drugs, AIDS trials, Chemical Identification, NIH Clinical Alerts, and a variety of other very useful access sites.

Specialized Information Services of the National Library of Medicine
http://sis.nlm.nih.gov/ToxSearch.htm
This provides a variety of information on toxicology and environmental health with searches and links to a variety of important organizations.

The Visible Human Project
http://www.npac.syr.edu/projects/vishuman/VisibleHuman.html
The Visible Human Project is a three-dimensional representation of the male and female body. The current phase deals with transverse CT, MR, and cryosection images at 1-mm intervals.

TOXNET ToxLine
http://toxnet.nlm.nih.gov/servlets/simple-search
This site provides free access for tox line searches. These include access to HSDB (Hazardous Substances Data Bank), CCRIS (Chemical Carcinogenesis Research Information System), RTECS (Registry of Toxic Effects of Chemical Substances), GENE-TOX [Genetic Toxicology (Mutagenicity) Data], IRIS (Integrated Risk Information System), TRI (Toxicology Releases Search), Chem-info (Chemical information identification), and many others.

Toxicology Environmental Health Information Program (TEHIP)
http://sis.nlm.nih.gov/tehipl.htm
This is the toxicology section of the National Library of Medicine that has a wealth of information that is searchable in many databases.

Environmental Chemicals Data and Information Network (ECDIN)
http://ecdin.etomep.net/Ecdin/E_hinfo.html
This is a factual database created by the European Commission, Joint Research Centre at the Ispra (I) site. It contains a list of chemical information for each chemical listed. One of its sections is PHATOX (Pharmacological and Toxicological) data which includes health evaluations, toxicological data, epidemiological data, and health hazard evaluations.

Karolinska Institute—Poisoning Information
http://www.mic.ki.se/Diseases/c21.613.html
The site provides access to many links with detailed information on a variety of poison issues including: general; bites and stings; food poisoning; gas poisoning; plant poisoning; lead, iron, mercury, cadmium, nickel, and drug poisoning; and hazardous substances. There are many pictures and multiple links.

The MedNet's Extensive Toxicology Database
http://www.internets.com/mednets/stoxicology.htm
This site provides a list of links to various toxicological sites.

Reprotox—An online reproductive toxicology resource
http://www.reprotox.org
Reprotox provides current assessments on potential harmful affects of environmental exposure to chemicals and physical agents on human pregnancy, reproduction, and development. This online source requires a subscription.

Pharmacy and Pharmaceuticals

Clinical Pharmacology Drug Database
http://www.cponline.gsm.com
Search engine for commonly prescribed drugs with dosages, indications, interactions, pharmacokinetics, costs, and more.

Dietary Supplements
http://odp.od.nih.gov/ods
This Web site provides information regarding dietary supplements.

Drug Database at Pharmaceutical Information Association
http://www.pharminfo.com
Information about pharmaceutical industry drugs and research from the Internet service PharmInfoNet.

Drugs of Abuse—Street Drugs
http://www.mninter.net/~publish/
This is a comprehensive collection of drugs of abuse. Although the information is somewhat basic it is very comprehensive.

Holistic Medicine
http://www.holisticmed.com/www
This is an interesting and very useful site that provides a lot of information on holistic medicines and alternative therapies.

Hyperreal
http://www.hyperreal.org
Important site that includes drugs of abuse primarily involving the "rave" scene.

Martindale Health Science Guide—The Virtual Pharmacy Center
http://www-sci.lib.uci.edu/HSG/Pharmacy.html
Access to Martindales pharmacy center for drug information.

Pharmacy (Medicine, Biosciences)
http://www.pharmacy.org
This site contains many links to pharmacy-related resources, including schools of pharmacy, online journals, CME, and societies.

PharmWeb
http://www.pharmweb.net
This is a searchable site from the U.K. with information for the patient and health professional.

Physician's GenRX Drug Compendium Program
http://www1.mosby.com/Mosby/PhyGenRx
A comprehensive listing that is searchable for generic or brand names and by drug category.

RxList Internet Drug Name Category Cross Index
http://www.rxlist.com
Searchable database of 4000 prescription and OTC drug products designed for the lay public.

ScripWorld Pharmaceutical News
http://www.pjbpubs.co.l;uk/acrip/scrhome.html
Scrip is the only international, twice-weekly newsletter reporting on the pharmaceutical sector, covering prescription and OTC medicines and biotechnology news.

Natural Toxins

American Zoo and Aquarium Association
http://www.aza.org
Information and pictures of toxic animals. Order form to obtain the Antivenom Index which is $20–30 in the publications area.

Antivenom Handbook for Australia
http://www.wch.sa.gov.au/paedm/clintox/cslb_index.html
This site has the handbook for a variety of poisonous animals from Australia. See the preceding site for North America.

Foodborne Pathogenic Microorganisms and Natural Toxins Handbook
http://vm.cfsan.fda.gov/~mow/intro.html
This is a site from the U.S. FDA Center for Food Safety and Applied Nutrition. Useful information on mushroom toxidromes.

Fungi Images on the Net
http://isa.dknet.dk/~pip1833/mushimage/
This a searchable Web site that contains information and photographs of various fungi, both poisonous and nonpoisonous.

Medical Botany Library
http://www.floridaplants.com/mpois.htm
Information on poisonous plants and mushrooms from around the world.

Medicinal and Poisonous Plant Databases
http://www.inform.umd.edu/EdRes/Colleges/LFSC/life_sciences/.plant_biology/Medicinals/medicinals.htm
Information and links on poisonous and medicinal plants from the University of Maryland.

NAMA—North American Mycological Association
http://Sorex.tvi.cc.nm.us/nama/poison/poison.htm
This is a very useful site that presents various mushroom toxidromes. There is also a case registry report form that can be downloaded and reported to NAMA.

Natural Toxins FDA
http://vm.cfsan.fda.gov/~mow/toxintoc.html
Lists information on fish, shellfish, mycotoxins, and many other natural toxins from the FDA.

Poison Information Centre—Singapore's Ministry of Health
http://www.gov.sg/health/mohiss/poison/index.html
Singapore's poison information center provides great information about natural toxins in their region of the world. The site also has pictures of many creatures.

Poisonous Plant Database (Plantox)
http://vm.cfsan.fda.gov/~djw/readme.html
The Poisonous Plant Database is a set of working files of scientific information about the animal and human toxicology of vascular plants of the world. The initial files were created in 1994, and are updated periodically.

Poisonous Plants Web Page of Cornell University
http://www.ansci.cornell.edu/plants/plants.html
This site provides information and pictures of poisonous plants. This site also lists veterinary species of interest.

The Poisonous Plant Guide
http://www.ednet.ns.ca/educ/museum/poison/ppguide.htm
An illustrated guide to some common poisonous plants in Nova Scotia including algae, fungi, and leafy plants.

Biochemical Terrorism

Anthrax Vaccine Immunization Program
http://www.anthrax.osd.mil/
The U.S. military's Web site for information related to the anthrax vaccination program. Includes information about anthrax and its use as a biological weapon, Q and A about the vaccine, a newsletter, and a section on related links.

Cal Poly Chemical and Biological Warfare Page
http:/www.calpoly.edu/~drjones/chemwarf.html
A page created by the students in the 1996 spring semester class of Chemistry 405. Contains documents on the history of chemical and biological warfare in ancient and modern times. Also contains sections on the nerve and riot control agents. Even shows the stepwise process of synthesizing several of the nerve agents.

CDC Bioterrorism Preparedness and Response
http:/www.bt.cdc.gov/
The CDC has dedicated a specific page within their Web site on bioterrorism. The page has two important sections for poison centers. The first is the Biological Agents section with a FAQ (frequently asked questions) document, Fact Sheet, Case Definition, and CDC Prevention Guidelines on a specific biological agent. The other section is the Learning Resources section. Included in this area are CDC resources such as articles on bioterrorism from the CDC Journal of Emerging Diseases, official statements on bioterrorism, a video library, and news and events. The video library contains two sets of tapes, the six-tape set from the September 1998 Medical Response to Biological Warfare and Terrorism and one tape from the Public Health Ground Rounds—*Bioterrorism: Implications for Public Health.* Watching the tapes requires the use of the Real Player program that is downloadable from the site.

Chemical and Biological Defense Information Analysis Center (CBIAC)
http:/www.cbiac.apgea.army.mil/
The center is located at the Battelle Memorial Institute and serves as the Department of Defense's focal point for information related to chemical warfare/chemical and biological defense. As part of its services, it offers an excellent search engine for the CBIAC site as well as password-protected bibliographic database (you can apply for a password online). Articles identified by a search in the bibliographic database are available only through the Defense Technical Information Center and have to be special ordered, which means setting up an account with them. However, the results of a search of the CBIAC site itself leads to documents that have unrestricted access.

FEMA Rapid Response Information System (RRIS)
http://www.rris.fema.gov/
Although this site is named "Rapid Response Information System" and it has a wide range of resources, it usually takes multiple screens to get to the information. The site has several sections including a relatively complete list of equipment with descriptions and vendors; an extensive list of monographs on nuclear, chemical, and biological agents; and a reference library with links to other sites and documents. There is also a symptom-based search engine that will find any symptom or group of symptoms names in the monographs.

EmergencyNET
http://www.emergency.com/
Web page for the Emergency Response and Research Institute. The site has separate pages for different EMS topics including Infectious Diseases and Chemical/Biological Terrorist Attack. The latter page contains a lesson plan for EMTs and First Responders regarding NBC incidents.

Medical NBC Online Information Server
http://www.nbc-med.org
Developed by the U.S. Surgeon General to provide a learning and reference resource for medical NBC information. Although the site has been developed for U.S. Army medical personnel, the site makes available many NBC health-related resources to any practitioner with access to the Internet. Site includes a news section, medical references (e.g., Army medical field manuals such as FM8-9(B) and the July 1998 edition of Medical Management of Biological Casualties), video and audio clips, training and calendar sections, and a search engine. Also there are numerous links to other NBC sites and many governmental and nongovernmental agencies involved with NBC information.

Mitretek Systems—Chemical, Biological, and Nuclear Systems
http://www.mitretek.org/mission/envene/nbc.html
This site has excellent monographs on the chemical and biological warfare agents (see Background on Chemical and Background on Biological Warfare Agents). The monographs are detailed with either chemical structures of the chemicals or toxins or photographs of the biological organism. Many other excellent references and documents related to chem/bioterrorism can be found as either onsite documents or links.

Outbreak
http://www.outbreak.org/
Outbreak is an online information service that addresses emerging diseases for the health professional and the interested layperson. It attempts to provide a worldwide collaborative database to collect information about possible disease outbreaks. There are registered user and nonregistered user portions of the site. There is the usual list of biological agents found at other sites with fact sheets for each one, but in addition, there are reports from ProMED about any past outbreaks of the disease. ProMED (Program for Monitoring Emerging Diseases), a list server from the Federation of American Scientists, provides information on emerging diseases via e-mail to its subscribers. Outbreak maintains a library of information about past outbreaks reported in ProMED.

Sarin Nerve Gas
http://www.geocities.com/CapCanaveral/Lab/7050/
Brief but informative site on sarin nerve agent. Describes sarin, its history as a terrorist agent, protective equipment, and dosage effects. Nice bibliography and links to other sites with reference documents on sarin.

The Chemical Weapons Conventions Web Site—Organization for the Prohibition of Chemical Weapons
http://www.opcw.nl/
Although this site's primary focus is the Chemical Weapons Treaty, there is an excellent section, Fact-finding Files, that gives accurate and even illustrated information on chemical and biological weapons. The main source for this information is the FOA Briefing Book on Chemical Weapons.

The John Hopkins Center for Civilian Biodefense Studies
http://www.hopkins-biodefense.org/
The primary value of this site is its summary of the National Symposium on Medical and Public Health Response to Bioterrorism held on February 16–17, 1999, in Arlington, VA. Many nationally recognized clinicians, both military and civilian, spoke at this conference along with many top government officials. The site contains the audio (you will need RealPlayerG2 on your computer to hear it) and PowerPoint slides from the conference. There are very brief written summaries of the presentations with the official publication of the conference proceeding appearing in the CDC publication *Emerging Infectious Diseases* Vol. 5, No. 4, the July–August issue (see http://www.cdc.gov/ncidod/eid/).

U.S. Army Research Institute of Chemical Defense (USAMRICD)
http://chemdef.apgea.army.mil/
The Army's center for chemical defense, USAMRICD Web page has several sections of interest. The first in an extensive bibliography by year of all the book chapters and published scientific papers produced by the USAMRICD staff. The next section of importance is a downloadable version of the Institute's 1995 edition of the Medical Management of Chemical Casualties handbook. The links section may not be functioning, but could be a good gateway to other sites.

U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)
http://www.usamriid.army.mil/
This is the home page of USAMRIID and a good site for two sources of information. First under its publications section, you can find downloadable versions of the Army's reference books, FM8-9 Handbook on The Medical Aspects of NBC Defensive Operations, Medical Management of Biological Casualties (July 1998 edition), and Defense Against Toxin Weapons. The second section of importance is the Continuing Education section which contains the text and PowerPoint slides used in the Army's Medical Management of Biological Casualties course.

U.S. Army Soldier and Chemical and Biological Defense Command
http://www.sbccom.army.mil/
Home page for the U.S. Army's Soldier and Chemical and Biological Defense Command. Best resource for description of military devices and products used in the detection and defense of a WMD release. Also has a description of the Domestic Preparedness training programs currently being administered by the Dept. of Defense.

WHO Communicable Disease Surveillance and Response (CSR)
http://www.who.int/emc/index.html
The primary value of this site is its monographs on various tropical diseases that could be potentially used as biological agents of terrorism. The monographs are relatively short but complete. There are also brief reports of outreaks of infectious diseases in various parts of the world.

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Policy Documents and Laws That Guide Clinical Pharmacy Practice in Spain

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INTRODUCTION

Clinical pharmacy practice in Spain is very closely linked to the concept of pharmaceutical care, as defined by Hepler and Strand:[1] "Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life." So much so, in fact, that the term *pharmaceutical care* already implies the concept of clinical pharmacy. The evolution toward pharmaceutical care implies the step in which the pharmacist *selects* the therapy, taking responsibility for it, instead of only *suggesting* it to the doctor.[2,3]

Originally introduced in hospital pharmaceutical practice, and although lack of human staff has prevented its consolidation at all hospitals, clinical pharmacy has grown throughout Spain in recent years. Pharmaceutical care, introduced more recently, is the current trend in hospital pharmacy, and is being increasingly adopted in community pharmacy practice.

Indeed, clinical pharmacy has become so important to pharmacy as a whole that it has now been included as an obligatory subject in pharmaceutical teaching and courses. Under the new educational plan, the second cycle of the pharmacy *licenciatura* (roughly equivalent to an honors degree) includes a central subject entitled "pharmacology and clinical pharmacy."[4] In 1984, a new European Community Directive (EC Directive 84/432) established that pharmacy undergraduate curricula should contain a 6-month stage in a community or hospital pharmacy. In the last year, the training period for hospital pharmacists has been increased by a year to a total of 4 years, an extra year dedicated exclusively to in-house clinical pharmacy training (the pharmacist visits the patients with the physician at the ward).[5]

The functions of the clinical pharmacist and the documents governing such activities in Spain are listed below.

GENERAL LAWS AND POLICY DOCUMENTS

There are a few documents that include nearly all functions developed by clinical pharmacists in Spain (see Table 1). They are, in chronological order, as follows.

Laws

Orden por la que se regulan los Servicios Farmacéuticos de hospitales (Ministerio de Sanidad y Consumo, 1977).[6] This is the law that primarily regulated hospital pharmacy services, defining for the first time some of the clinical activities that the pharmacist must develop, such as drug information, clinical trials, or pharmacovigilance.

Ley General de Sanidad (Ministerio de Sanidad y Consumo, 1986).[7] This is a general law that regulates most subjects health-related, including all health service structures and requirements for drug commercialization, as well as some of the pharmacist's functions as a healthcare provider.

Ley del Medicamento (Ministerio de Sanidad y Consumo, 1990).[8] In force since 1990, it represents the most important law in the drugs area. It regulates most clinical activities developed by pharmacists at any health institutions.

Policy Documents

Coloquios de aproximación a la farmacia clínica (Asociación Española de Farmacéuticos de Hospitales, 1981).[9] This document collects the conclusions of eight debates about clinical pharmacy in which participated 200 hospital pharmacists, including subjects such as drug selection, drug information, and pharmacist integration in

Table 1 Clinical content in general laws and policy documents that guide clinical pharmacy in Spain

Type of document	Title, publication year, reference	Drug selection	Drug information	Pharmaco-kinetics	Artificial nutrition	Clinical trials	Drug use	Pharmaco-vigilance	Other
Laws	Orden 1 febrero, 1977[6]	No	Yes	No	No	Yes	No	Yes	No
	Ley General de Sanidad, 1986[7]	No	No	No	No	Yes	No	Yes	No
	Ley del Medicamento, 1990[8]	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Policy documents	Farmacia Hospitalaria, 1990, 1992[10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Manual del Residente, 1999[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	SEFH Practice Guidelines and Consensus Statements[13,15,17,19,30]	Yes	Yes	Yes	Yes	No	No	No	Yes

the healthcare team. The impact of this document reached Europe through the Eighth European Symposium on Clinical Pharmacy, held in Lyon, France, in 1979.

Farmacia hospitalaria (Sociedad Española de Farmacia Hospitalaria, 1990).[10] Edited in 1990, this book compiles all activities, clinical and nonclinical, developed by an hospital pharmacist. Due to the success of the first edition, two years later, the contents were reviewed, and a second edition was published, including more details about clinical contribution of the pharmacist on patient's pharmacotherapy.

Acreditación docente de servicios de farmacia hospitalaria (Sociedad Española de Farmacia Hospitalaria, 1991).[11] Elaborated by the National Speciality Commission, this document contains the acreditation requirements for a hospital pharmacy service to be able to train future specialists, as well as the program of hospital pharmacy specialization. In 2000, the program was revised to include one more year dedicated exclusively to clinical pharmacy training.[5]

Manual del residente de farmacia hospitalaria (Sociedad Española de Farmacia Hospitalaria, 1999).[12] Elaborated to by a consult handbook for future specialists, all teaching hospitals participated in its creation; it contains most activities developed by the hospital pharmacist, with theory and practical cases.

SEFH consensus statements, practice recommendations, and guidelines (Sociedad Española de Farmacia Hospitalaria). As any society, the Spanish Society of Hospital Pharmacy (SEFH) periodically publishes practice recommendations to facilitate its members' work and daily practice at hospital. They include some clinical areas such as pharmacokinetics, artificial nutrition, and drug information (see below).

THE CLINICAL PHARMACIST'S AREAS OF ACTION

Drug Selection

Law: *Ley General de Sanidad.* Ministerio de Sanidad y Consumo, 1986.[7]

Art. 95.5. "All people who work at health services must collaborate in drug evaluation and control. . . ."

Law: *Ley del Medicamento.* Ministerio de Sanidad y Consumo, 1990.[8]

Art. 84.4. and 84.6. "Public Administration will proceed for primary and specialized care structures to make a scientific drug selection and evaluation, through Drug and Therapeutics Committee . . ." and ". . . will promote the publication of drug formularies for healthcare professionals' use."

Art. 91.2. "Hospital pharmacy services will take part in hospital commissions to participate in drug selection and evaluation according to evidence, and drug use."

Policy document: *SEFH Recommendations: Drug formulary edition.* Sociedad Española de Farmacia Hospitalaria, 1994.[13]

Through this document, the SEFH defines the concept of drug formulary and tries to give a guide in how to

elaborate it. It must contain the drugs selected by the Drugs and Therapeutics Committee with their basic information, institutional proceedings regarding drug prescription, and practical drug information such as drugs in pregnancy and lactation, dose adjustment in renal or hepatic impairment, drug interactions, and so on.

Further information provided by the SEFH about drug selection in hospitals is compiled in Chapter 2.1 of the book *Farmacia Hospitalaria*.[14]

Drug Information

Law: *Ley del Medicamento*. Ministerio de Sanidad y Consumo, 1990.[8]

In primary healthcare

Art. 87. "Functions that guarantee the rational use of drugs: drug information to health-care professionals; drug information to patients, drug monitoring and pharmacovigilance; promotion and participation in educating the general public about drugs, their rational use and the prevention of abuse. . . ."

In hospital and specialized care

Art. 91.2. "To achieve the rational use of drugs, the hospital pharmacy services shall: establish a drug information service for all hospital staff, organize educational activities dealing with issues in their field addressed to healtcare staff at the hospital and their patients. . . ."

Policy document: *Procedural regulations regarding drug information*. Sociedad Española de Farmacia Hospitalaria, 1996.[15]

This is a guide with recommendations on how best to perform the basic duties at a Drug Information Center (CIM). Individual CIMs adapt the recommendations in line with their specific features. CIM directors should be qualified pharmacists.

According to the SEFH, one of the basic functions of a CIM is to evaluate and transmit information concerning drugs. The following recommendations are considered particularly important:

- A regular information procedure should be established on new developments in pharmacotherapy for the pharmacy service staff and technical advice for the dispensation unit concerning any medication-related problems detected.
- Priority should be given to aspects such as efficiency, safety, and cost when technical reports to drug-selection committees are being prepared.
- Active information will be education- and training-oriented and will be addressed to healthcare staff via bulletins and to patients.
- Passive information in response to enquiries will be as objective, concise, useful, and clear as possible.

More complete details about a hospital pharmacist's activities concerning information on drugs and the functions of the CIM are given in Chapter 2.4 of the book *Farmacia Hospitalaria* (Hospital Pharmacy) by the SEFH.[16]

Clinical Pharmacokinetics

Law: *Ley del Medicamento* (Ministerio de Sanidad y Consumo, 1990).[8]

Art. 91.2. "To achieve rational use of drugs, hospital pharmacy services shall carry out clinical pharmacokinetic activities. . . ."

Policy document: *SEFH recommendations on inical pharmacokinetics* (Sociedad Española de Farmacia Hospitalaria, 1997).[17]

The SEFH recommends that a hospital's clinical pharmacokinetic unit should form part of the pharmacy service and be directed by a pharmacist specializing in hospital pharmacy. It defines the functions of this unit as the following:

- Drug selection to be included in the pharmacokinetic monitoring program, on the basis of narrow therapeutic margin and extensive pharmacokinetic variability.
- Selection of patients to benefit from this program.
- Selection of analytical methods on the basis of specificity and sensitivity.
- Interpretation of plasma levels depending on the characteristics of the drug, the patient's clinical data, and concomitant treatment.
- In cases where dosage needs to be modified, the pharmacist informs the doctor in charge of the new dosage, when it should be started, if any doses should be avoided, the expected plasmatic levels, and subsequent analytical controls, if necessary.

Chapter 3.2 of *Farmacia Hospitalaria* (Hospital Pharmacy) contains a more detailed description of these activities.[18]

Artificial Nutrition

Policy document: *SEFH recommendations on artificial nutrition* (Sociedad Española de Farmacia Hospitalaria, 1997).[19]

The SEFH considers artificial nutrition to be multidisciplinary in range and scope and, therefore, recom-

mends the creation of Artificial Nutrition Commissions, in which the pharmacy service should be always and actively represented. The main task of these Commissions is to establish an artificial nutrition protocol that includes:

- Records of enteric nutrition, peripheral parenteral nutrition, and central parenteral nutrition.
- Assessment of nutritional state.
- Calculation of calorie requirements.
- Administration routes.
- Biochemical monitoring.
- Standard formulas and regulations governing individual prescriptions.

In the SEFH's view, the preparation and dispensation of artificial nutrition is not the pharmacy services' only activity, as they can also perform prescription and clinical monitoring. This already occurs at a number of Spanish hospitals: the pharmacist prescribes and performs daily checkups on patients being fed artificially.

Policy document: *Nutritional therapeutics* (Sociedad Española de Farmacia Hospitalaria, 1992).[20]

This chapter describes the activities performed by the pharmacist as a member of the nutritional support team, which involve a range of tasks from indications, assessment of nutritional state, and the preparation of artificial nutrition for adults and children to concepts on basic dietetics and mother–infant nutrition. Drug–nutrient interaction analysis is another duty.

Clinical Trials

Law: *Ley del Medicamento* (Ministerio de Sanidad y Consumo, 1990).[8]

Chapter 3 (Art. 59-69) is devoted entirely to clinical trials. Besides the duties of dispensation and control of clinical trial samples, the hospital pharmacist's clinical duties in this area arise from his participation as a member of the CEIC, Spain's Ethical Clinical Research Committees.

Art. 64.2. "The committee shall consider the methodological, ethical and legal aspects of the proposed protocol, and the balance of risk and benefits expected from the test."

Art. 64.3. "The CEIC shall, at the very least, consist of an interdisciplinary team involving doctors, hospital pharmacists, clinical pharmacologists, nursing staff and several people unconnected with any of the healthcare professions, one of whom, at least, shall be a jurist."

Law: *Real Decreto establishing the requirements for performing clinical trials with drugs* (Ministerio de Sanidad y Consumo, 1993).[21]

Heading 3 deals with CEIC. Art. 41.2 emphasizes that the hospital pharmacist should be a member of the CEIC, and Art. 42 describes the duties and functions of the CEIC: "...to evaluate the protocol and the research team, evaluate the written information to be given to the subjects of the research, perform monitoring of trials...."

Policy document: *Clinical trials* (Sociedad Española de Farmacia Hospitalaria, 1992).[22]

Involving the pharmacist in the clinical trials may actually facilitate the work in some aspects, including:

- Patient monitoring and follow-up, in which the pharmacist collaborates with the researcher in the compilation of analytical parameters.
- Registering and channeling any adverse reactions observed and trying to establish the causal relation.
- Conveying information to the patients to help them comply properly with the protocol.

Drug Use Evaluation and Pharmacoepidemiology

Law: *Ley del Medicamento* (Ministerio de Sanidad y Consumo, 1990).[8]

Art. 91.2. "To ensure the rational use of drugs the hospital pharmacy services... shall prepare reports on drug use... and perform any duties that lead to improved drug use and control."

Policy document: *Pharmacoepidemiology and drug use evaluation* (Sociedad Española de Farmacia Hospitalaria, 1992).[23]

Types of drug use evaluation reports, postmarketing pharmacovigilance trials and economic appraisal in the context of pharmacoepidemiology are described.

Pharmacovigilance

Law: *Ley General de Sanidad* (Ministerio de Sanidad y Consumo, 1986).[7]

Art. 99. "Importers, manufacturers and healthcare professionals are obliged to inform on all adverse reactions caused by drugs and medical devices, whenever there is a risk to the life or health of patients."

Law: *Ley del Medicamento* (Ministerio de Sanidad y Consumo, 1990).[8]

Art. 57.1. insists on the obligation to declare unexpected or toxic effects of drugs.

Art. 58.3. "Doctors, veterinarians, pharmacists, nurses and other healthcare professionals shall be obliged to collaborate in the Spanish Pharmacovigilance System."

Pharmacovigilance is one of the functions of both the primary health care pharmacist (art. 87) and the hospital pharmacist (art. 91.2).

The SEFH has signed a Collaboration Agreement with the Spanish Ministry of Health and Consumer Affairs to promote and encourage the hospital pharmacist's participation in the Spanish Pharmacovigilance System, which includes, among other things, using the "yellow card" system to notify any adverse drug reactions.[24]

Law: *Circular 18/90 de la Dirección General de Farmacia y Productos Sanitarios*, 1990.[25]

Includes several guidelines on preparing pharmacovigilance trials.

Other Clinical Activities of the Hospital Pharmacist

Published by the SEFH in 1992, *Farmacia Hospitalaria* covers other specific duties of the clinical pharmacist in the health system, such as clinical toxicology[26] and clinical activities in hospital clinical units: infectious diseases, pediatrics, oncology, gynecology, surgery, geriatrics, clinical hematology, cardiovascular, intensive care units, psychiatry, emergencies, etc.[27]

Activities in Community Pharmacy

Law: *Ley de regulación de servicios de las oficinas de farmacia* (Jefatura de Estado, 1997).[28]

Art. 1: Enumerates the functions and duties of pharmacists working in pharmacy offices, which include "information and follow-up of pharmacological treatment of patients; collaboration on the control of individualized use of drugs to detect any possible adverse reactions and inform the relevant pharmacovigilance bodies."

Since the law came into effect, the community pharmacist has evolved from a mere "pharmaceutical adviser" to becoming involved in the launch of pharmaceutical care programs.

Policy document: *Granada Consensus on drug-related problems*, 1998.[29]

On the assumption that the three basic objectives of pharmaceutical care are to identify, solve, and anticipate medicinal drug-related problems, the Consensus of Granada established a classification of such problems based on the application of a systematic criterion of evaluation of the requirements of pharmacotherapy: to be indicated, effective, and safe.

OTHER DOCUMENTS

Spanish Code of Pharmaceutical Ethics (Commission on Bioethics and Pharmaceutical Ethics, Sociedad Española de Farmacia Hospitalaria, 1998).[30]

This is a consensus document promoted and prepared by a task force from the SEFH and accepted by other organizations, including the *Sociedad Española de Farmacéuticos de Atención Primaria* (Spanish Association of Primary Healthcare Pharmacists), the *Consejo General de Colegios Oficiales de Farmacéuticos* (General Council of the Official Colleges of Pharmacists), and the *Real Academia de Farmacia* (Royal Spanish Academy of Pharmacy). This code of ethics includes the basic principles and responsibilities of the pharmacist in his relations with the patient, other health care professionals, and society in general.

Web Sites on Clinical Pharmacy/Pharmaceutical Care

An increasing number of Web pages of interest to the clinical pharmacist are appearing on the Internet, including the following in Spain:

- Atención Farmacéutica (Pharmaceutical Care), Carlos III Health Institute, National Health School, http://www.isciii.es/unidad/Sgpcd/ens/atenfar/paginaprincipal. htm.
- *Club de Atención Farmacéutica* (Pharmaceutical Care Club), Pharmacy Faculty, University of Granada, http://www.ugr.es/~atencfar/welcome.htm.
- *Atención Farmacéutica* (Pharmaceutical Care), Cinfa laboratories, http://www.atencion-farmaceutica.com/.
- *Unidad de Farmacia Clínica y Farmacoterapia* (Clinical Pharmacy and Pharmacotherapy Unit), Pharmacy Faculty, University of Barcelona, http://www.ub.es/farcli/wp0.htm.
- *Fundación Pharmaceutical Care España*, Barcelona, http://www.pharmaceutical-care.org.

Journals on Pharmaceutical Care/Clinical Pharmacy

The following are a few journals pertaining to pharmaceutical care and clinical pharmacy:

- *Farmacia Hospitalaria (Farm Hosp).* Sociedad Española de Farmacia Hospitalaria. http://www.sefh.es/revistas/revistas.htm.
- *Atención Farmacéutica—European Journal of Clinical Pharmacy (Aten Farm).* http://www.farmaclin.com.

- *Pharmaceutical Care España (Pharm Care Esp).* Fundación Pharmaceutical Care España. http://www.pharmaceutical-care.es.

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29. Panel de consenso ad hoc. Consenso de Granada sobre problemas relacionados con medicamentos. Pharm. Care Esp. **1999**, *1*, 107–112.
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Post-Marketing Surveillance

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INTRODUCTION

The United States has one of the most rigorous drug approval processes in the world, but 51% of marketed drugs have serious adverse effects that are not detected during pre-marketing clinical studies.[1] Consequently, post-marketing surveillance is required to collect data about drugs or other medical products once they are available to the general population.[2] Post-marketing surveillance in the United States is the responsibility of the Food and Drug Administration (FDA). Pharmacovigilance expands on the concept of post-marketing surveillance and is the continuous process of evaluation accompanied by steps to improve safe use of drugs.[3] Both post-marketing surveillance and pharmacovigilance involve pharmaceutical companies, regulatory authorities, healthcare providers, and patients. This monograph provides an overview of the post-marketing surveillance process in the United States including a justification of need; the roles of the FDA, drug manufacturers, healthcare providers, and patients; and strengths and weaknesses of the current system.

JUSTIFICATION OF NEED

Pre-marketing clinical studies are only expected to detect adverse drug events (ADEs) with an incidence of 0.1% or greater; the ability to detect those with an incidence between 0.1% to 1% is unreliable.[4] Limitations of pre-marketing clinical studies include their short duration and use of surrogate endpoints rather than clinical outcomes. In addition, pre-marketing clinical studies are conducted in well-defined study populations, for one indication, and with limited concomitant medications. Finally, the number of patients exposed to the drug during pre-marketing clinical studies is generally between 3000 and 4000. An ADE with an incidence of 0.01%, may require a study population of 30,000 patients to have a 95% chance of detection.[5]

The Prescription Drug User Fee Act of 1992 (PDUFA) and the FDA Modernization Act of 1997 (FDAMA) have been credited with reducing clinical development and regulatory review times from 30 to 12 months.[6] Consequently, the percent of products first available in the United States has increased.[7] Less than one-third of new drugs were previously first introduced in the United States; drug events in other countries served as an ADE early warning system. Although a decrease in review time and an increase in first available products has raised safety concerns,[8,9] the frequency of labeling changes for serious adverse events has decreased from 52% in the 1980s to 30% in the 1990s.[10] Furthermore, the rate of safety-based market withdrawals of new molecular entities has not changed; ranging from 1–3.5% over the past several decades (Fig. 1).[6]

POST-MARKETING SURVEILLANCE PROCESS

At the center of the current U.S. post-marketing surveillance process is the FDA (Fig. 2); drug manufacturers, healthcare providers, and patients are also vital to the success of this process. Currently, only the roles of the FDA and drug manufacturers are defined by statute. The role of hospitals in reporting ADEs is defined by the Joint Commission on Accreditation of Healthcare Organizations[11] and of hospital pharmacists by the American Society of Health-System Pharmacists.[12] For an index of U.S. federal regulations and guidelines that covers safety surveillance of drugs, the reader is referred to an article published by Curran and Engle.[13]

Food and Drug Administration

The FDA has operated a post-marketing surveillance program since 1961, replacing a system operated by the American Medical Association. The FDA currently receives more than 250,000 ADE reports yearly.[14] Within the FDA, the Center for Drug Evaluation and Research (CDER) Office of Post-marketing Drug Risk Assessment (OPDRA) is responsible for post-marketing surveillance. The objectives of the post-marketing surveillance program are to detect ADEs not previously observed, to

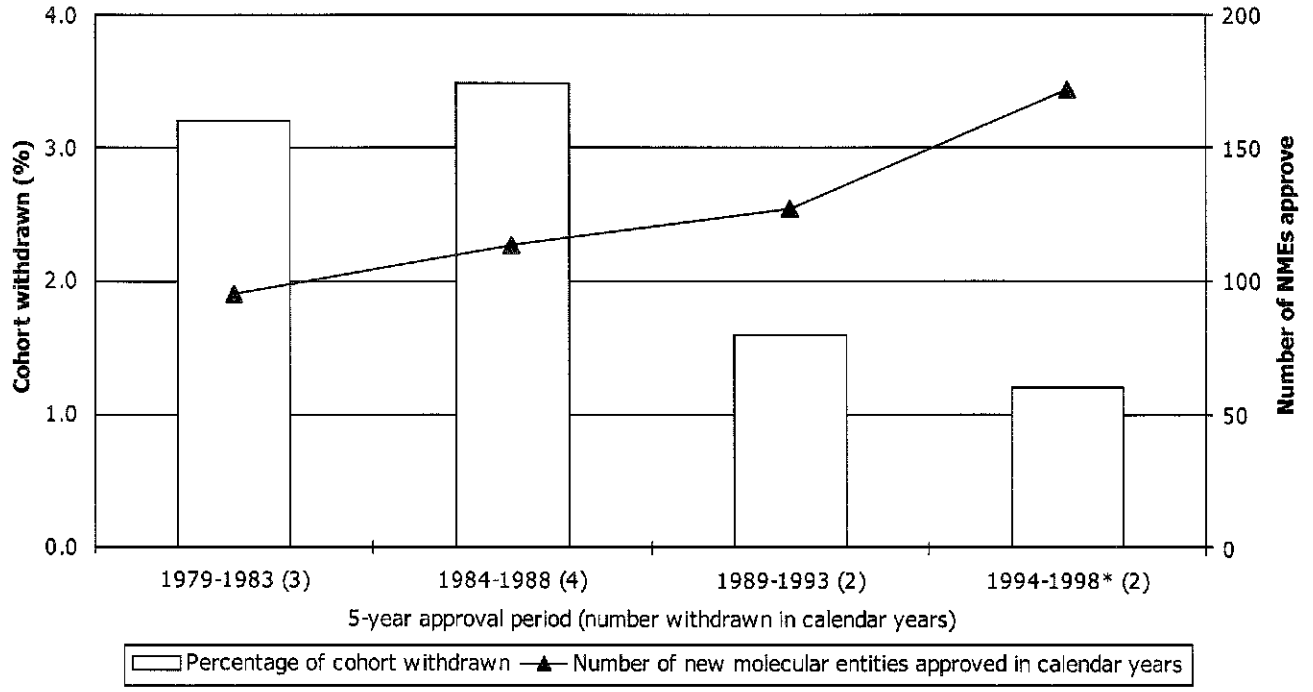

Fig. 1 New molecular entity withdrawals. NME, new molecular entity; *Prescription Drug User Free Act years. (From Ref. [6].)

improve the understanding of the potential severity of previously anticipated risks, to detect events resulting from drug interactions or drug effects in particular populations, and to assess the potential for causal relationships.[6] The FDA's primary mechanism for identifying serious ADEs is the spontaneous reporting system (SRS). Additional approaches include the use of large healthcare databases, cohort and case-control studies, and product registries.

In 1993, the FDA introduced a new streamlined SRS, MedWatch. MedWatch allows healthcare providers and patients to report ADEs to the FDA by several mechanisms, including electronic and print media (Table 1). The goals of the MedWatch program are to increase awareness of drug- and device-induced disease, clarify what should be reported to the FDA, simplify the reporting process, and provide regular feedback to the healthcare community about safety issues involving medical products.[15]

Information received through the MedWatch program is entered into the Adverse Event Reporting System (AERS) database. The AERS database is designed to permit electronic or paper submission of reports, comply with international standards and terminology, and facilitate pharmacovigilance screening. In addition to the MedWatch program, the FDA runs a program for adverse events related to veterinary products and in conjunction with the Center for Disease Control and Prevention, a program for adverse events with vaccines, the Vaccine Adverse Event Reports System (VAERS).

After determining that a problem exists through the post-marketing surveillance process, the FDA has several options. These options include medical alerts such as "Dear Health Professional" letters or safety alerts published in the FDA Medical Bulletin or on the MedWatch web site, press releases, product labeling changes, boxed warnings, and product withdrawals. The FDA may also require a drug manufacturer to conduct post-marketing safety studies. It should be noted that the FDA is only able to request that a manufacturer remove a product from the market.

Drug Manufacturers

Drug manufacturers may identify ADEs through several means, including spontaneous reports by healthcare providers or patients, clinical studies, and reviews of the medical literature. Once the company is aware of an ADE, the data are evaluated, the seriousness and ex-

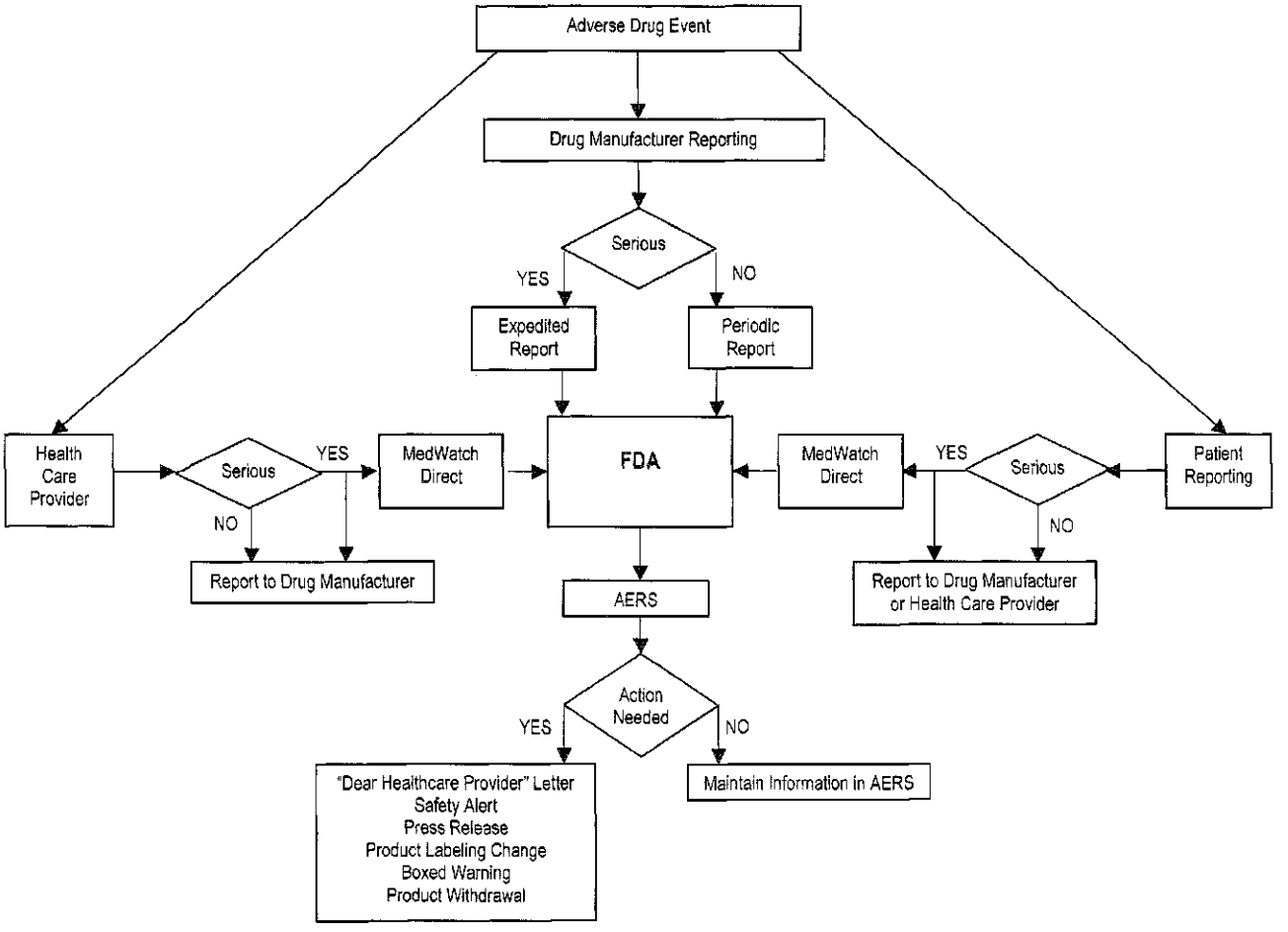

Fig. 2 Post-marketing surveillance process. An ADE is serious if the outcome is death; life-threatening; requires an intervention to prevent permanent impairment or damage; or results in hospitalization, disability, or congenital anomaly. AERS, Adverse Event Reporting System. (From Ref. [16].)

pectedness are determined, and a report is submitted to the FDA (Fig. 2). Approximately 75% of all reports received by the FDA are either expedited or periodic reports from drug manufacturers (Fig. 3). The process for notification of the FDA by a drug manufacturer is defined by the Federal Code.

The Federal Code describes two levels of ADE reporting for drug manufacturers. The first level of reporting is an expedited report for serious or unexpected events reasonably attributed to the drug. These events require submission of a 15-day alert report. The drug manufacturer is also required to submit a 15-day alert report when an increased frequency of an ADE or of drug failure is noticed. The second level of reporting is a periodic report for all ADEs attributed to the drug. These periodic reports are submitted quarterly for the first 3 years a drug is marketed and yearly thereafter.

Healthcare Providers

Voluntary reporting of ADEs by healthcare providers is invaluable to the post-marketing surveillance process (Fig. 2). These reports often provide the first signal to the FDA that a problem exists. Whereas only serious ADEs should be reported to the FDA, all ADEs can be reported to the drug manufacturer. An ADE is classified as serious if the outcome is death; life-threatening; requires an intervention to prevent permanent impairment or damage; or results in hospitalization, disability, or congenital anomaly.[16] The reporting healthcare provider needs only suspect an association between the drug and ADE; causality of the event does not need to be determined. In all cases, healthcare providers need to provide complete and accurate details of the ADE.

Table 1 Contacts for adverse event reporting

Method	Contact
MedWatch	
Direct mail	MedWatch The FDA medical products reporting program Food and Drug Administration 5600 Fishers Lane Rockville, MD 20852-9787
Facsimile	1-800-FDA-0178
Internet	https://www.accessdata.fda.gov/scripts/medwatch/
Modem	1-800-FDA-7737
Telephone	1-800-822-1088
VAERS[a]	
Internet	http://www.fda.gov/cber/vaers/vaers.htm
Telephone	1-800-822-7967
Veterinary Products	
Telephone	1-888-332-8387

[a]VAERS = Vaccine Adverse Event Reports System.

Patients

The role of the patient is also vital to the post-marketing surveillance process, particularly in identifying an ADE in an outpatient setting. Although patients may report serious ADEs directly to the FDA or any ADE to the drug manufacturer, it is suggested that they work through a healthcare provider who may be able to more accurately assess the ADE.[17]

WEAKNESSES AND STRENGTHS OF CURRENT SYSTEM

The current post-marketing surveillance system involves multiple processes and interactions. A breakdown in any one of these processes or interactions could lead to a weakness. Several weaknesses of the current system have been identified. The first is the identification of an ADE. Identification of an ADE is subjective and imprecise.[18] A study to evaluate how accurately ADEs are identified, found less than a 50% agreement between clinical pharmacologists and treating physicians.[19] A second weakness of the current system is underreporting of ADEs. The FDA estimates that only 1–10% of ADEs are reported.[20] A third weakness is the introduction of bias. ADEs reported through the SRS are not subjected to the same rigorous standards as those determined through controlled clinical studies. These reports are therefore subjected to a number of biases, including the length of time a product has been marketed, reporting environment, detailing time, and quality of data.[21] A fourth weakness is the inability to estimate population exposure to the drug. The FDA attempts to overcome this weakness by forming cooperative agreements with outside research organizations. Unfortunately, these data still need to be interpreted cautiously because drug prescribing may not equal drug usage.[22] The fifth weakness of the current system is the

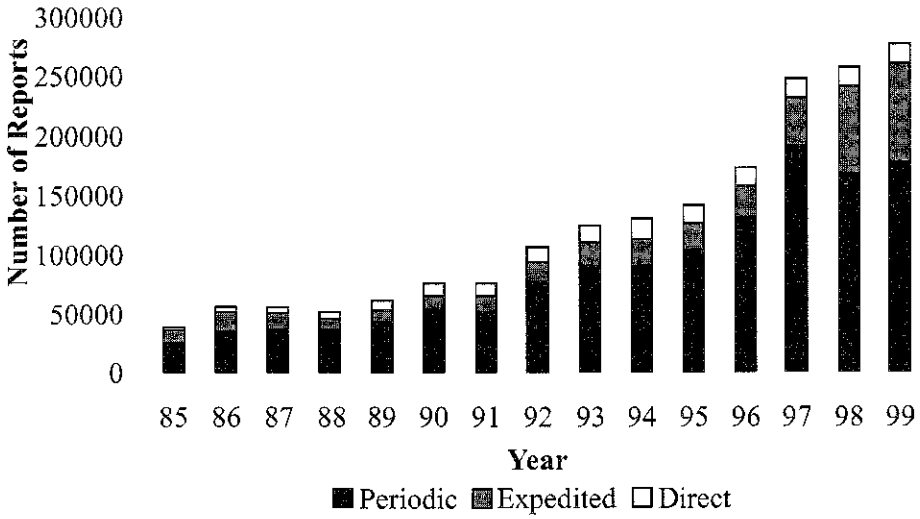

Fig. 3 Number of periodic, expedited, and direct reports received by the FDA for the years 1985–1999. (From Ref. [14].)

quality of reports submitted to the FDA. Often the poor quality of information received does not allow the FDA to adequately evaluate the report and be proactive in protecting the public.[6] The final weakness of the current system is the lack of effect of the FDA's action. A study documented that the prescribing habits of cisapride did not change after the FDA expanded the black box warning, issued a press release, and had the manufacturer distribute 800,000 "Dear Health Professional" letters.[23]

In spite of these limitations, the current system does have some strengths. For example, it covers large numbers of diverse patients. Reports generated through the SRS reflect everyday use of the drug. A second strength of the system is the ability to monitor ADEs in an inexpensive manner. The current system is relatively inexpensive compared with an observational event monitoring system.[24] The last strength of the current system is its ability to generate hypotheses and signals. Currently, the FDA is in the process of determining what constitutes a signal; this strength is only beginning to be fully used.

FUTURE DIRECTION OF POST-MARKETING SURVEILLANCE

The future direction of the FDA's post-marketing surveillance process is to strengthen and expand the current system. To increase the ability to identify ADEs, the FDA is piloting a "sentinel" system that uses a small subset of healthcare institutions and charges them with preparing frequent, detailed ADE reports. To increase the number of reported ADEs, the FDA is increasing its education programs. Improvement in physician knowledge of ADEs was reported after a 2-year program of sustained physician education. This was accompanied by a 17% increase in the number of ADE reports submitted.[25] To more rapidly investigate potentially serious ADEs, the FDA is evaluating a plan that would increase their access to usage and event data through large healthcare databases.

In addition to those items previously mentioned, the FDA is also participating in the development and use of international standards to facilitate pharmaceutical development. The goals of the International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH) is to facilitate the mutual acceptance of data submitted in support of drug marketing applications by the European Union, Japan, and the United States. The ICH has developed a number of guidelines and standards to harmonize post-marketing surveillance efforts on an international level.[26]

In addition to those items developed by the FDA, the creation of an independent center for assessing pharmaceutical effectiveness has been proposed.[1,27,28] This center would be an independent agency that would assist in developing answers to issues that face healthcare providers and patients after a drug has been marketed, including therapeutic differences and safety issues.

CONCLUSION

The current post-marketing surveillance system in the United States is a multifaceted, international process involving the FDA, drug manufacturers, healthcare providers, and patients. Whereas the FDA is strengthening the current system, its success will still rely heavily on the submission of spontaneous reports. Therefore, healthcare providers need to be continually reminded of the value of reporting ADEs.

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Prescriptions for Health: The Lowy Report

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INTRODUCTION

Prescriptions for Health, commonly referred to as the Lowy report after its chairman, was initiated by a provincial government after noting astronomical rises in its health care expenses on prescription drugs (20% annually and 500% over the past decade). The report contains 147 recommendations, many directed at government, but many also directed at the health professions, the health science centers, the pharmaceutical manufacturers, distributors, and the public. The report was produced by a committee appointed by the Ontario Ministry of Health. Its members were F. Lowy (Chair), M. Gordon, R. Moulton, R. Spunt, J. Thiessen, D. Webster, and W. Wensley. (Members Thiessen and Wensley are pharmacists.)

MAJOR CONCLUSIONS

The committee found that Ontarians receive "excellent treatment involving prescription drugs" and that they were safe, available, and affordable through insurance plans and government-supported programs for the aged and those receiving social welfare. However, the committee went on to note some problem areas:

- Some products paid for by the government plan were suboptimally effective or had unfavorable benefit/risk ratios.
- Physicians are not well prepared educationally for prescribing the many agents available, especially for the elderly; CE programs were found lacking.
- Pharmacists were "not meeting their full professional potential as members of the health care team."
- Some citizens do not have access to these drugs, because they are the "working poor" without insurance or have extraordinary drug costs because of catastrophic illness.

The committee found less than adequate cooperation between the federal government (responsible for approving new drugs on the market) and provincial governments (responsible for managing drug programs for seniors and those on social assistance).

Recommendations are directed at government, medicine, hospitals, nursing, and the public; the following is a synopsis of those recommendations involving pharmacy:

4.22: The continuation of drug interchangeability whereby pharmacists provide the generic equivalent (defined) of the lowest-cost product acceptable to government. This is followed by a number of other recommendations regarding drug pricing and the development of the concept of "best available price."

6.8: That unit-dose/IV admixture be the system of choice for institutional drug delivery in hospitals and that the Ministry aid hospitals in the costs of conversion.

7.4: That physicians and pharmacists jointly study the appropriateness of the quantity of drugs on a prescription and prepare guidelines.

7.7: That postmarketing surveillance studies be established involving large numbers of family physicians and others.

7.9: That "Choice of Medications—1990" be made available to all physicians and pharmacies and that it contain guidelines and objective information on drug prescribing.

7.11 and **7.12**: That the hospital formulary system be fostered and that the concept be extended to group clinics, nursing and old age homes, health maintenance organizations, and comprehensive health organizations.

7:13: That generic names be on all prescription labels.

7.15: That a pilot project be established to test the Harvard model of academic detailing.

7.18: That physicians and pharmacists establish formal mechanisms on the issues of patient counseling and communication.

8.1: That the role of pharmacy assistants be defined and ensure that they perform product-oriented tasks while

DOI: 10.1081/E-ECP 120006270

pharmacists concentrate on patient-oriented tasks such as monitoring drug therapy and providing advice to patients and other health professionals.

8.2: That information management systems be established to ensure optimal access to patient profiles and adverse drug interaction programs.

8.3 and **8.4**: That standards for original packaging dispensing be developed.

8.5: That auxiliary labels and other printed information on prescription drugs along with verbal be increased, with reinforcement by the pharmacist.

8.6: That pharmacists pay particular attention to the visually handicapped when labeling.

8.7: That pharmacists label in the language of the patient, with verbal reinforcement.

8.8: That a campaign be aimed at seniors to pick one pharmacy for all services.

8.9: That patient profiles be required in all community pharmacies.

8.10: That portable patient medication records such as the "smart card" be developed.

8.11: That guidelines be developed to ensure the pharmacist has access to the patient's diagnosis(es).

8.12: That a campaign be launched to make the public more aware of the services to be expected of a pharmacist, especially those related to the provision of information on proper use.

8.13: That all pharmacies have a private and comfortable consultation area.

8.14 and **8.15**: That pharmacists exert more control over the sale of nonprescription drugs.

8.16: That pilot projects be established to assess alternative reimbursement for the provision of pharmaceutical services not based on the sale of a drug.

8.17: That linkages involving the patient be developed between the medication profile in hospital and in the community.

8.18: That the clinical role of pharmacists be encouraged and expanded in monitoring and intervention as necessary.

8.19: That pilot projects of community drug therapy committees be established, modeled on institutional settings.

8.20: That drug information programs be supported and expanded.

8.22: That a second faculty of pharmacy, with a five-year curriculum, be established.

8.22: That the present faculty of pharmacy (U. Toronto) increase its curriculum to five years with more instruction on patient counseling, therapeutics, drug information, pathophysiology, and geriatrics.

8.24: That the practical training period be restructured.

8.25: That a PharmD program be established in two years.

8.26: That joint teaching occur in medicine and pharmacy on patient-oriented services, including therapeutics, monitoring techniques, and patient counseling.

8.30: That pharmacy services to long-term institutions be improved.

8.31: That pharmacy and nursing work out their roles in counseling.

8.36: That mechanisms be put in place to ensure appropriate patient education regarding treatment plans prior to discharge.

8.37: That all hospital pharmacies require patient profiles.

8.39: That mechanisms be established to compensate hospitals providing pharmacy services to outpatients.

8.41: That funding be increased for hospital pharmacy residencies.

8.42: That standards and ethically appropriate methods of cost containment be established for investigational drugs.

8.45: That community programs for patient compliance be funded.

9.3: That drug utilization review programs be integrated into medical CE.

9.4: That the provincial adverse drug reaction program be supported.

9.6: That approaches be researched to reduce use of hypnotics, sedatives, and tranquilizers.

11.1: That liquid formulations be provided to the elderly with swallowing difficulties.

11.2: That smart cards be introduced to facilitate monitoring and that pharmacy computer systems be programmed to handle problems of the elderly.

11.5: That guidelines be developed to limit hypnotics, sedatives, and tranquilizers for the shortest possible time with no repeats.

INFLUENCE

Eleven years later, many of the recommendations have been carried out, at least partially. Others have not moved significantly since the report's publication. Probably the most important aspect of the report was the laundering of the province's medication system in public, with responsibilities being levied at our government, our universities, and our professions. Yet, although the highlights of this report may have hit the lay press for a day or two, particularly the aspects of drug pricing, there is little long-term effect. The provincial pharmacy associations have taken the report seriously and have initiated many of its recommendations.

The initial concern of the government and the committee, namely, a rapidly climbing total drug bill, has only been partially addressed. Efforts have been made to control drugs such as omeprazole through the "limited use" requirement, which places additional (unpaid) work on pharmacists. Significant efforts have also been made in some pilot projects on antibiotic prescribing; the model involves joint educational efforts for community physicians and pharmacists and joint efforts to follow guidelines on a variety of infectious diseases. In areas where these efforts have been started, antibiotic costs have fallen by 10–20%. However, overall in the province, the drug budget continues to gallop ahead at the rate of 12% per year.

The report is as relevant today as it was a decade ago. It recognized the valuable work of clinical pharmacists in institutions and recommended that it be extended not only in institutions but into the community as well. The development of the PharmD programs at the University of Toronto (in Ontario) and the University of British Columbia (farthest western province) has provided further stimulus to this effort. Standards (hospital accreditation, hospital pharmacy, and community pharmacy) also seem to have been influenced or minimally have paralleled the recommendations of this report.

Because Ontario is Canada's most populated province, events that occur there are often considered by other provinces or in national efforts. It is therefore fair to suggest that the Lowy report probably had significant influence beyond the boundaries of Ontario.

CONCLUSION

All in all, we would do well do revisit these recommendations, particularly those dealing with seamless care and computerized records. The patient orientation urged by Lowy for pharmacists has certainly spurred the clinical movement in this part of the world.

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PROFESSIONAL DEVELOPMENT

Preventive Medicine

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INTRODUCTION

Health Promotion and Disease Prevention: Definitions and Concepts

In the health sciences field, preventive medicine has traditionally been defined as the ensemble of actions and advice aimed specifically at preventing diseases[1–4] and promoting health, and the process for enabling individuals and communities to increase their control over the determining factors involved in health to improve it.[5] Besides health-restoring activities, there are also those that are fundamentally preventive such as immunization, health education for healthy people, and screenings.

As Hogarth[7] pointed out, over the last few years the meaning of the term *preventive medicine* has expanded considerably. It is being applied more and more to the health activities organized for defending and promoting the population's health at the community level. Those who accept this broad definition of preventive medicine equate it with health promotion. For them, preventive medicine would comprise all the preventive activities of the public health services that concern the individual (vaccination of a child, case finding in a healthy adult, health education through the conversation during the visit, including also certain aspects of pharmaceutical care) or collective (immunization campaigns, collective health check-ups, population screening, mass media health information and education campaigns, etc.). All these actions concern the individual and are carried out by health services, physicians, pharmacists, and qualified nurses, on the basis of knowledge furnished by medical science.

Today, what we understand as health protection is the health promotion and defense actions concerning the environment (environmental health and food hygiene) and it is carried out by public health professionals (veterinarians, pharmacists, biologists, health engineers, etc.) on the basis of scientific principles furnished not only by medicine but also by other sciences (health engineering, architecture, food hygiene and technology, etc.).[6]

In short, as Last[8] pointed out, the term *preventive medicine* in its broadest sense implies a more personal encounter (immunization, screening, health education) between the individual and the medical or pharmaceutical personnel than that entailed in health protection activities (potabilization and fluoridation of mains water, processing of milk, sewage disposal, etc.), since in the latter case the professionals have no contact at all with the user.

THE NATURAL HISTORY OF DISEASE

Any disease or morbid condition is the result of a dynamic process. The causative agents or risk factors present in the environment interact, after a variable period of incubation with the host (whose greater or lesser susceptibility to the disease is conditioned to a large extent by genetic factors) and cause the disease. Leavell and Clark differentiate three defined periods in the natural history of the disease: the prepathogenic period, the pa-

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006386

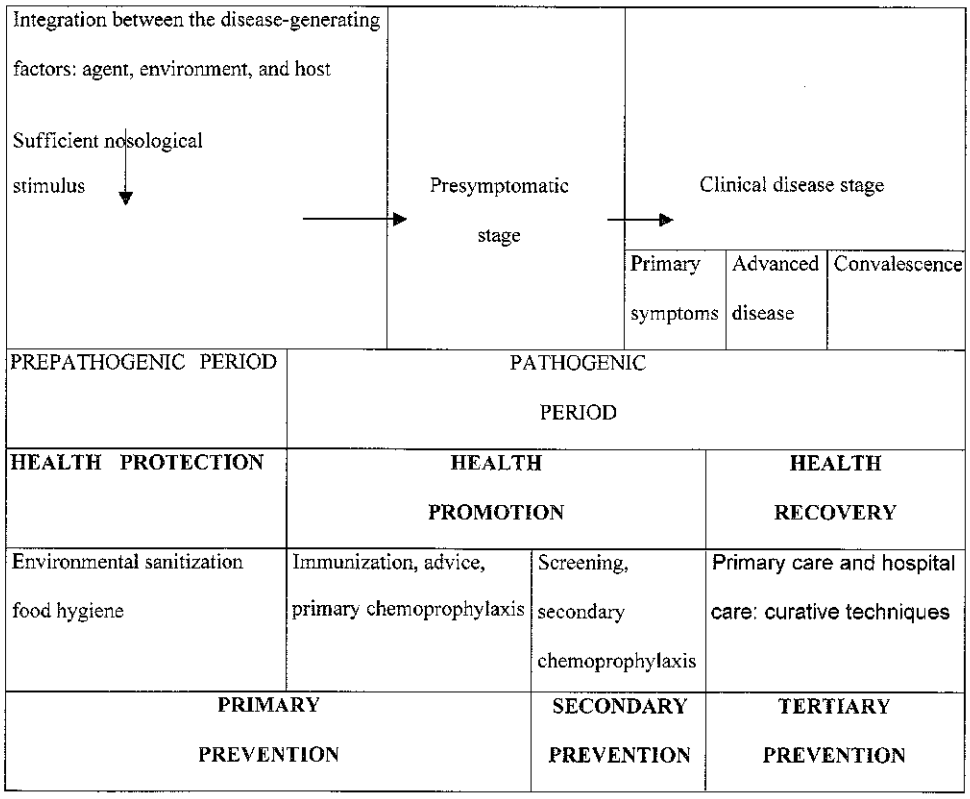

Fig. 1 Natural history of disease and levels of prevention. (From Ref. [9].)

thogenic period, and the result[9] (Fig. 1). This division is of great interest, as we see later in the article with regard to the levels of prevention.

Prepathogenic Period

The prepathogenic period is characterized by the presence of factors that favor or determine the development of the disease. These factors may be environmental (infectious, physical, chemical agents, etc.) and behavioral (overconsumption of fats or carbohydrates, sedentary lifestyle, smoking, excess consumption of alcohol, use of illegal substances, etc.), and they affect the endogenous genetic predisposition[2–4] toward developing the disease.

Some of these factors are necessary (but not sufficient) for the onset of the disease. The clearest example is that of the agents of infectious diseases (bacteria, viruses, etc.). At other times, the factors are not absolutely necessary for disease onset, as this can occur in their absence, although their presence implies an increased likelihood of the condition arising. Such is the case with the risk factors for chronic diseases (high blood pressure, obesity, smoking, hypercholesterolaemia, etc.).[2–4]

It should be noted that the existence of a close statistical relationship between a risk factor and a disease does not mean that all individuals with the risk factor will necessarily develop the disease, or that the absence of this risk factor is any guarantee that the disease will not develop.

Pathogenic Period

The pathogenic period has two stages: the presymptomatic stage and the clinical disease stage. During the presymptomatic period, there are no symptoms or clinical signs but, as a result of the causal stimulus, the anatomical and pathological changes responsible for the disease (arteriosclerosis in the coronary arteries, premalignant disorders in the tissues, etc.)[10] are already under way.

In the clinical stage, the changes in the organs and tissues are already important enough for signs and symptoms of the disease to appear in the patient.[10]

Finally, the result is the last period in the natural history of the disease and reflects the end of the process: death, disability, chronicity, or recovery.

PREVENTIVE ACTIVITIES: LEVELS OF PREVENTION

Application of the concept of "levels of prevention" is possible because, as mentioned earlier, all diseases in their natural history present more or less defined periods during each of which it is possible to apply some form of preventive measures.[2]

Although preventive medicine experts do not fully agree on the limits required between each of the levels that can be established, their differences are more semantic than essential.[6,7]

At present, preventive activities are classified into three levels: primary, secondary, and tertiary prevention levels,[7] as shown schematically in Fig. 1.

Primary Level of Prevention

The aim of primary prevention is to reduce the probability of disease occurring. From the epidemiological viewpoint, it aims to lower their incidence.[7] Primary prevention measures act during the prepathogenic period of the disease's natural history before the interaction of the risk factors and/or agents with the host produces the stimulus that triggers the disease.

Currently, a distinction is usually made between two types of primary prevention activities: those for health protection, which are applied to the environment, and those for health promotion and disease prevention, which are applied to people. Preventive activities, then, are really those that affect people; that is, health promotion and disease prevention activities carried out by health professionals and teams in primary health care.

Health protection is oriented toward the environment and includes activities aimed at controlling the causal factors of the disease that are present in the general environment (environmental sanitization), the work environment (safety in the workplace), or in food (food hygiene).

Health promotion and disease prevention are oriented toward people. With disease prevention, the idea is to reduce the incidence of specific diseases by means of specific actions exercised by health professionals, generally within the framework of primary care, although they can also be applied in other areas (schools, factories, etc.). With health promotion, the idea is that people themselves should adopt favorable lifestyles and give up unhealthy habits through educational intervention (health education in schools, factories, primary care centers, and pharmacies, and via the mass media) and legislative measures.

Secondary Level of Prevention

Secondary prevention takes place once the disease-triggering stimulus has occurred and acted, as the only preventive possibility is to interrupt or delay progress of the condition by detaining it with the appropriate, early treatment, with the aim of curing it or preventing it from becoming chronic and preventing the onset of sequelae and invalidity.[11–13] From the epidemiological viewpoint, secondary prevention aims to reduce the prevalence of the condition or disease. The basic assumption of secondary prevention is that early diagnosis and treatment improve disease prognosis and management.

The increase in chronic conditions in developed countries during the twentieth century has aroused a great deal of interest in the early detection of disease. In such diseases, in the majority of which primary prevention is very difficult or impossible, the strategy of the health services must be to aim for early detection to treat them as soon as possible and improve the prognosis. To solve the problem of the delay in detecting chronic diseases the application of different selection processes (screenings) has been proposed to detect them in asymptomatic persons.

Tertiary Level of Prevention

Tertiary prevention comes into play when the pathological lesions are irreversible, the disease is well established and the chronic phase has passed, and whether or not sequelae have appeared (somatic or mental functional limitation).[7] The proposed objective is to slow the course of the disease and alleviate any disability when it arises.[8]

In all this process, the pharmacist has traditionally been associated to health protection activities. More recently, however, everyone agrees on the pharmacist's role in the field of health promotion and disease prevention: the pharmacist should incorporate, in daily practice, screenings and health advice for the people attended to in the pharmacy.

ROLE OF THE COMMUNITY PHARMACIST IN HEALTH PROMOTION AND DISEASE PREVENTION

Pharmaceutical Care

Essentially, the activity of community pharmacists—that is, pharmacists who provide pharmaceutical care for the community from the pharmacy—is based on the purchase, storage, and dispensing of drugs, making up extemporaneous preparations, pharmacotherapeutic follow up of patients, and advice about drugs and health problems.[14,23]

Table 1 Importance of community pharmacy in health promotion and disease prevention

1. Community pharmacy is frequently the first contact with the health system: high frequency of contacts with low barriers to access (no appointments, no long waiting time, convenient opening hours, located within communities, information readily on display, etc.).
2. Community pharmacy reaches the broad population: they see a wide range of potential target groups within the patients/clients/users (people with incidental needs, people with chronic illness, healthy people, people from all social strata).
3. Community pharmacy contacts have a good potential to integrate the social environment into counseling (geographic distribution, positioning on the "high street," principal shopping areas, etc.). Contacts take place often and normally on a regular basis and include interactive, communicative, and counseling aspects.
4. There are a large number of experts, pharmacists, and other qualified staff working in community pharmacy, offering a high level of competence and knowledge of medicines.
5. Health issues are already on the agenda of the users of community pharmacies, and the pharmacists are considered experts in a variety of health issues and often actively provide a link to other health professionals, mostly to general practice doctors.
6. Community pharmacy can offer a balanced mix of contributors to curative care, prevention, rehabilitation, and health development.

(From Ref. [23].)

Over the last few years, applying the criteria of pharmaceutical care, pharmacists have extended their activity to embrace other health interventions associated with improving people's quality of life. In 1993, within the framework of the International Pharmacists Congress, FIP'93,[15] the Declaration of Tokyo was approved. In that declaration, pharmacists gave the definition of pharmaceutical care and stated that the patient is the principal beneficiary of their actions. *Pharmaceutical care* is defined as the ensemble of attitudes and actions involving medication and the role of the pharmacist as a health agent. The main implication arising from this viewpoint was the conviction that pharmaceutical care must be developed as an integral part of health services.

The objective of pharmaceutical care in the community is to participate in health promotion, disease prevention, and education. The declaration also proposes specific spheres of action: the rational use of drugs; smoking cessation; and advice on vaccination, hygiene, family planning, AIDS prevention, etc. Even now, pharmacists have still not fully developed their potential as health agents within this health system,[16] but the community pharmacy is of specific importance for health promotion (Table 1).

Specific Programs of Preventive Activities in Community Pharmacy

In practice, health promotion from the community pharmacy has been described in different studies published since 1950, although more frequently since 1980 and, specifically, in studies conducted in England and Canada.

In 1993, the Health Education Authority and the National Pharmaceutical Association published "Health Promotion and the Community Pharmacist",[17] which serves as a practical guide for all health promotion activities that can be carried out by British pharmacists from the community pharmacy.

Along the same lines, another publication to be noted is "Pharmacies and Smoking Cessation",[18] which within the WHO's European program plan of action for a tobacco-free Europe was started in 1993 in pharmacies in Denmark. The result being that, at present, 20% of Danish pharmacies routinely offer a smoking cessation service for their population.

In Catalonia (Spain), in 1997, a consensus among the Department of Health's experts in preventive medicine, nursing, and pharmaceutical scientific associations was attained. It was decided to initiate a process to implement[13] different activities in the community pharmacies in Catalonia (Table 2). These activities have been chosen according to the health plan priorities. The most important point is that these activities are carried out with collaboration with the health care teams of primary health care centers. It was first implemented as a "training trainers" procedure and now these activities are carried out in most pharmacies in Catalonia since 1997.[1,19,20]

Also in Catalonia—Barcelona to be specific—the Pla Farmacèutic d'Educació Sanitària[19] (Pharmaceutical Plan for Health Education), drawn up by the Barcelona

Table 2 Specific preventive activities in Catalonia's community pharmacies

1. Screening for high blood pressure.
2. Screening for excess weight and obesity.
3. Screening for hypercholesterolaemia.
4. Advice on drug use and self-medication.
5. Advice on active immunization.
6. Advice on preventing sexually transmitted diseases and AIDS.
7. Advice on giving up smoking.
8. Dietary advice.
9. Advice on preventing mouth and teeth diseases.
10. Advice on, and prescription of, physical exercise.
11. Advice on excess alcohol consumption.
12. Advice on screening for breast cancer and cervical cancer.

(From Ref. [1].)

Pharmaceutical Association, proved the viability of health education in both the therapeutic and health promotion spheres. Three hundred pharmacists took part in the experiment in Barcelona, the educative sessions being attended by around 10,000 people. The evaluation proved the value of exercise as it helped to significantly increase the knowledge of those attending about the matters discussed.

Also to be noted are the two health education plans drawn up in Spain by the Consejo General de Colegios Farmacéuticos (General Council of Pharmaceutical Associations), with the collaboration of the provincial associations: the Plan de Educación Nutricional (Plan for Education on Nutrition)[21] and the Plan de Educación sobre el medicamento (Plan for Education on Drugs).[22]

Requirements to Carry Out Preventive Activities in the Community Pharmacy

For the pharmacy pharmacist to be able to carry out the health promotion and disease prevention activities with due rigor and consistency, and for these activities to be well coordinated in primary health care, it is necessary to perform the following:

1. Give priority to activities that, in healthy adults, have shown to be effective in the population; that is, they have provided some health benefit for the community and constitute a framework of reference that makes it clear which preventive activities should be carried out at the pharmacy.
2. Adapt the joint development of these activities to the needs and programs established for each basic health area. The idea resulting from all this is that there has to be coordination between all the agencies and professionals involved in primary health care, and the appropriate supports and mechanisms for achieving this coordination.

In practice, to carry out the preventive activities defined, the pharmacist will have to take into account the need for the following:

1. Reinforcing knowledge, skill, and attitude through accredited, continued training.
2. Creating an atmosphere and place for these activities.
3. Having the necessary measuring equipment and resources for the activities.
4. Setting a good example, both the pharmacist and the other personnel, to reinforce the aforementioned healthy atmosphere.

Table 3 What can health promotion offer to the community pharmacy?

- Increase impact and effectivessnes of pharmacotherapy
- Increase impact and effectivessnes of counseling and health-related advice
- Increase job satisfaction by job enrichment:
  - By fostering liaison with users
  - By improving cooperation with other providers
  - By making visible "the cognitive service" information, advice, and counseling
- Make the contribution of community pharmacy evident
  - In the management of drug therapy
  - As an important place for health-related service
- Support the integration of community pharmacy into the primary health care team

(From Ref. [23].)

5. Organizing, recording, and establishing protocol for the activities to evaluate them in accordance with the quality criteria established and divulge the results.
6. Using the communication currents established with the appropriate graphic supports for the purpose of exchanging information (Appendix 1) with the primary care team of the health areas.

Applying health promotion principles could be a means to further develop the professional role (Table 3).

CONCLUSION

Health promotions activities in primary health care, in general practice and in community pharmacy, is not yet well documented or evaluated with sufficiently high quality standards. There seems to be a wide variance in the degree to which health-promoting services, projects, and programs are documented, evaluated, and evidence based. In particular, there seems to be need for further work concerning lifestyle counseling, health education, and interventions for health development.[23]

The need to be able to evaluate the effectiveness of the activities is obvious. Therefore, it will be essential to specify, during the process of implementing health promotion at the pharmacy, what the particular objectives are and which activities must be carried out, while ensuring that the former are attainable and the latter feasible on the basis of the resources available. It will be necessary to plan a careful implementation strategy that will ensure the participation of as many professionals as possible while also permitting evaluation of the repercussions, on the population's health, of the integration of health promotion activities into the pharmacist's practice.

APPENDIX 1

Servei Català de
la Salut

Consell de Col·legis
Farmacèutics de Catalunya

INTER-CONSULTATION FORM

From **pharmacy** ☐

primary care centre ☐

(full name and address)
telephone number

To **primary care centre** ☐

pharmacy ☐

(full name and address)
telephone number

Patient's data

1st surname 2nd surname name

Reason for consultation

Comments on the reason for consultation

Stamp and signature Date:

Report from the department consulted (if necessary)

Stamp and signature Date:

NCR paper

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Primary Care, Clinical Pharmacy Services in (ACCP)

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INTRODUCTION

Health care reform has renewed the interest in primary care. Major problems with America's health care system include escalating health care costs, maldistribution of health care providers into urban areas, lack of health care insurance, and the excessive utilization of specialists. These issues have assured that health care reform will take place. At the time of this report, the nature and format of a reform plan has not been determined. Nevertheless, many agencies are rapidly evaluating their current health care coverage and are preparing for the inevitable reform that will take place.

There have been disproportionately high numbers of medical specialists compared with generalists since the 1960s.[1] Worldwide, there are approximately five to six generalists for every subspecialist. For various reasons, perhaps most importantly, economics, this ratio is reversed in the American health care system. For well over 20 years, governmental agencies and medical academicians have tried to increase the numbers of primary care providers without significant success. With millions of underinsured Americans, the provision of primary care has become a national priority. Clinical pharmacists must become more involved in the provision of primary patient care. Most clinical pharmacists, however, have not viewed themselves as primary care providers and, therefore, may not feel adequately prepared to become a member of an interdisciplinary primary care team.

This article is an extension of a previous American College of Clinical Pharmacy (ACCP) White Paper on Clinical Pharmacy Practice in the Noninstitutional Setting.[2] That white paper described the functions that should be expected of clinical pharmacists in ambulatory care settings. This article assists practitioners and administrators who want to establish and evaluate services in ambulatory care and primary care settings. This article presents approaches to define the scope of a pharmacist's practice and obtain clinical privileges, evaluate the process of delivering care, evaluate patient outcomes related to pharmacotherapeutic decisions, and define the legal implications of providing primary patient care.

DEFINITIONS

There is considerable confusion in pharmacy concerning current definitions of practice sites and practice philosophies. *Ambulatory care* includes all health-related services in which patients walk to seek their care.[1] These services may be provided in emergency rooms, urgent centers, private offices, primary care clinics, specialty and subspecialty clinics, and community pharmacies.

Primary care is a subset of ambulatory care with unique features and philosophies.[1] (By definition, inpatient care is never a primary level of care.) One set of definitions,[3] suggests that primary care is a form of care that includes:

1. "First-contact" care, serving as a point-of-entry for the patient into the health care system;
2. Continuity by virtue of caring for patients over a period of time, both in sickness and in health;
3. Comprehensive care, drawing from all the traditional major disciplines (medical specialties, nutrition, and social) for its functional content;
4. The assumption of continuing responsibility for individual patient follow-up and community health problems; and
5. Highly personalized care.

Dr. Elizabeth Short of the Veterans Administration (VA) Central Office has stated, "Primary care is the coordinated, interdisciplinary provision of health care that consists of health promotion, disease prevention, comprehensive management of acute and chronic medical and mental health conditions, and patient education. A primary care physician coordinates access to and integration of other components of health care, such as inpatient, long-term, or subspecialty care, and psychosocial support. Un-

From *Pharmacotherapy* 1994, 14(6):743–758, with permission of the American College of Clinical Pharmacy.

DOI: 10.1081/E-ECP 120006411

der primary care, a provider or provider team is the primary source of a patient's care, and the place that a patient turns to for health care information and support."[4]

The key feature of primary care clinicians is that they handle a wide range of medical conditions. They serve as the entry point into the health care system and decide on referral or triage to secondary or tertiary levels of care. Specialty clinics provide ambulatory care, and, in many cases, some primary care. Most specialists (e.g., cardiology, neurology, nephrology, etc.), however, are considered secondary levels of care. These secondary and tertiary levels of care should be utilized when a problem is beyond the expertise of the primary care clinician. The typical family practice physician or general internist cares for well over 90% of problems that present to them. There is a small percentage of problems that would require referral to secondary or tertiary care. Even when a patient is referred for a specific problem, the primary care clinician should maintain overall care for the patient and coordinate all other aspects of care. This continuity implies chronic care and preventive care that are more conducive to long-term assessments of patient outcomes than can be achieved with acute illness managed in the inpatient setting.[3]

Clinical pharmacists and pharmacotherapy specialists provide care in a wide variety of ambulatory care and primary care settings.[1,2] There are two major types of practice that are very distinct. While currently more common in structured settings such as hospitals and health maintenance organizations, primary care is increasingly being provided in many settings including community pharmacies. The first type of practice is one in which the pharmacist is *independently responsible for providing primary care*, typically between regularly scheduled physician visits. This includes conducting complete histories; obtaining objective information including physical assessment and ordering laboratory tests; starting, stopping, or changing drug therapy; and determining the appropriate timing of follow-up visits. These activities are common in pharmacist-managed clinics in the Indian Health Service, medical centers, and VA hospitals, including hypertension, diabetes, hyperlipidemia, anticoagulation, and pharmacy service clinics. These activities are in contrast to those provided by other professionals such as physician assistants or nurse practitioners who may perform functions traditionally performed by a physician.

The second type of setting is an *interdisciplinary team approach* to care of the patient where the pharmacist sees patients with physicians. Pharmacists who work in such teams assist with care at the same time other health professionals see the patient. In this setting, they may have independent patient care activities but these would not be as extensive as are generally seen in pharmacist-managed clinics. These settings would include family practice offices, general medicine clinics, or pediatric clinics.

ESTABLISHING AN AMBULATORY CARE OR PRIMARY CARE PRACTICE

Obtaining Clinical Privileges

Prior to any patient intervention, it is essential that the clinical pharmacist has in place a document that outlines specifically the practitioner's scope of practice.[5] It is important that the scope of this document be sufficient to allow the clinical pharmacist to function as a member of an interdisciplinary primary care team. This document could be in the form of clinical privileges or a scope of practice statement (Appendix 1). This approach could be used for developing a practice for a new practitioner or used for a previous clinician who has not formally obtained scope of practice privileges. If the facility is an organized health care center (hospital or managed-care organization), it would be worthwhile to review the facility's guidelines for clinical privileges granted to the physician's assistants and/or nurse practitioners if these are available. Depending on the institution, approval is required by the Chief of Pharmacy, Chief of Staff, Clinical Executive Board, and the Institutional Director. Once these privileges are established, only then can the clinical pharmacist provide primary patient care (e.g., in pharmacist-managed clinics).

In the past, formal guidelines to obtain clinical privileges were often not commonly developed in private practice or other settings such as outpatient family practice settings. However, clinical pharmacists in private practice, community pharmacies, family practice residencies, and health maintenance organizations should develop these guidelines for their clinical pharmacy practitioners to ensure quality and evaluate performance. For clinicians in these settings, it is less likely that formalized arrangements for scope of practice privileges exist with physicians or other health professionals. However, similar templates as those for institutions (Appendix 1) could be used and modified for these settings.

The application form in Appendix 1 also requests data on whether the clinical pharmacist is board certified in pharmacotherapy or another specialty. Board certification should be considered strongly desirable, if not required. At the present time, the most appropriate specialty certification process for ambulatory or primary care pharmacists would be certification in pharmacotherapy. This would be analogous to physician certification in the broad-based specialty of family practice. Board certification in pharmacy will be increasingly important and it

should be achieved by all ambulatory care/primary care pharmacy practitioners who provide the services outlined in this report.

QUALITY OF CARE PROVIDED BY PHARMACISTS IN PRIMARY CARE: EVALUATING PROCESS AND OUTCOMES OF PATIENT CARE

A comprehensive discussion of quality of care assessments is beyond the scope of this paper. This area of assessment, however, will become increasingly important in the near future. This report is intended to provide the pharmacist who practices in ambulatory care with an understanding of basic principles used to assess quality. For more in-depth reviews in this area, the reader is referred to the references and the Appendixes.

There is a great deal of interest in measuring or assessing patient outcomes. As Donabedian points out, however, outcomes can only be assessed within the overall context of health care.[6] For instance, the therapy that a pharmacist selects may have minimal influence, or perhaps even a detrimental influence on patient care, depending on the care of other practitioners, demographic factors, and the interpersonal relationship. Donabedian maintains that quality can only be assessed by examining the three components: structure, process, and outcome.[6] He suggests that there must be a knowledge of how structure and process are linked, and how outcome and process are linked before quality assessments can be made. Structure not only refers to the facility, its services and its location, but also the number and characteristics of the providers. For providers this would mean whether they are in solo or group practice and whether they are board certified.[6,7] For physicians it has been shown that board certification is a predictor of good process, but only by implication, of good outcomes. Process refers to what is done for the patient in providing care.[6,7] This includes making diagnostic and treatment decisions. Outcome refers to what happens to the patient and this may include the patients' knowledge or satisfaction with care.

Lohr and Brook have stated that quality of care is composed of both technical care and the art of care.[7] The art of care includes the practitioner's ability to provide reassurance, obvious concern of the patient's well-being, good counseling, and sensitivity to the patient. As examples, they cite whether the provider introduces himself to the patient, refers to the patient specifically by name, announces and/or explains activities before or while doing them (such as physical examination), and says goodbye to the patient. Obviously, these are all critical factors to address if patient satisfaction is being assessed. Providing these personal services is not new but it is increasingly important when patient satisfaction drives third-party contracts in managed care. Pharmacists must provide these personal levels of care if they truly are delivering pharmaceutical care.

Evaluating the Process of Delivering Care

Performing quality assurance evaluations of specific pharmacists' performance does not measure patient outcomes, but rather, the process of delivering care. However, providing an acceptable or ideal process (or standard of care) should, by implication, create an environment conducive to better patient outcomes. However, to move from evaluating process to evaluating outcome, other specific tools must be used (see below). Appendix 2 is an example of a quality assurance form that might be used in a pharmacist-managed primary care clinic.

Guidelines are being developed for a wide range of disease states and conditions. These essentially describe processes for delivering care. They can be used by the individual clinician to prospectively guide appropriate therapy. In contrast, they can be used retrospectively as a quality assurance measure. Appendix 3 lists 12 disease states that are critical to outpatient primary care, and that are currently the most common conditions cared for by pharmacists in primary care settings. While these are not all-inclusive, they provide examples that can be followed in other therapeutic areas. Where possible, nationally accepted clinical practice guidelines are provided for each of these disease states. It is imperative that clinical pharmacy practitioners be aware of nationally accepted guidelines for specific conditions they may treat in their settings. The importance of this is discussed below.

The Agency for Health Care Policy and Research (AHCPR) was created by Congress to be the successor of the National Center for Health Services Research. This agency explores medical conditions that affect large populations, have multiple therapeutic interventions, and have a large economic impact. Through the Medical Treatment Effectiveness Program (MEDTEP), the AHCPR examines variations in health care practices on patient outcomes.[8] The MEDTEP involves patient outcomes research, clinical guideline development, scientific data development, and research dissemination. The agency has supported the development of numerous guidelines such as the guidelines for depression and for angina.[9] The AHCPR is currently developing practice guidelines for the effective therapeutic management of asthma, arthritis, hypertension, and congestive heart failure. In addition to this federal agency, private groups

such as the American College of Physicians, the American Medical Association, the BlueCross BlueShield Association, and other specialty societies are developing new treatment guidelines.

It is important to note that AHCPR is not a regulatory agency and is not involved with reimbursement. Application of the guidelines is not enforced by the government. Using these guidelines that were prepared by multidisciplinary panels of experts may allow primary care providers to deliver scientifically sound care to the patient.

There are also medical-legal issues pertaining to clinical practice guidelines developed by specialty societies. The general counsels who are involved with these issues, private practice attorneys, and the counsel of the American Medical Association generally believe that following established clinical practice guidelines would be a strong defense in malpractice cases. However, if a practitioner deviated widely from these guidelines, he or she would need to have a strong rationale, documented in the patient's record, to support the use of an alternate regimen.

A major issue that needs to be addressed is what standards or methodologies should be followed when guidelines are developed.[10] A structured, systematic, science-based approach should be used whenever developing these guidelines. The Institute of Medicine has identified the necessary characteristics which would enhance a guideline's effectiveness: sensitivity, specificity, patient responsiveness, readability, minimal intrusiveness, feasibility, and computer compatibility.[11,12] If guideline development followed these scientific methods, it would be difficult to criticize the process.

In contrast to good guideline development, the determination of whether guidelines are useful depends upon their readability, computer compatibility, and other factors. Outcomes management takes the results of the outcomes research and incorporates them into clinical practice guidelines to theoretically help ensure all patients receive the most effective treatment available.[11,12]

Assessing Health Outcomes

Another objective of this report is to determine the best method to measure the impact of pharmacotherapeutic decisions made by clinical pharmacists on patient outcomes. There are several approaches that can be used to assess outcomes. These include disease- or treatment-related outcomes (e.g., blood pressure, seizure frequency, medication adherence, target serum concentrations). The Task Force felt that it was not appropriate for this report to delineate specific clinical outcomes such as level of blood pressure control or serum drug concentrations. While these are important outcome measures, the Task Force wanted to highlight optimum methods for documenting positive outcomes of clinical pharmacy interventions. To keep in step with health care reform, a good method of assessing the impact of therapy on a specific chronic disease is health-related quality-of-life (HRQL) outcome measures. The pharmaceutical industry, the medical profession, and governmental agencies have shown increasing interest in assessing new measures of a drug's overall effectiveness. Quality of life (QOL) will be considered as seriously as safety and efficacy when evaluating response to therapy.

Even when primary care providers follow accepted clinical practice guidelines, there is no assurance of a favorable outcome. That is why it is important for the clinical pharmacist to understand and use appropriate, clinically relevant outcome measures to quantify the impact of their interventions.[12] Bungay and Wagner argue that HRQL outcome measures should assess physical, social, and role functioning; emotional distress and well-being; general health perceptions; and energy and fatigue.[13] They also stress that the assessment of health status must be integrated into the care of patients. HRQL measures can be used to assess a population with a specific disease, or as a research method to examine how changes in process affect outcomes.[14] The current challenge is to develop tools and operations that can be used in the office setting to evaluate care, and hopefully direct treatment for individual patients. It is critical, however, that these assessments be performed while considering the patient mix, timing of data collection (timing during the evolution of a disease process), patient characteristics, and measurement properties. The reader is referred to a more comprehensive discussion of these issues.[14,15] We will briefly discuss the importance of HRQL outcomes, the types of instruments available, and how to choose a specific instrument for a specific patient population.

Quality of life includes many issues occurring in a person's life, such as health status, job satisfaction, family issues, and overall well-being.[6,7,14,15] Since these are nonspecific, this measurement may not be the best indicator of positive or negative pharmacotherapeutic interventions made by a clinical pharmacist. Health-related quality-of-life assesses those aspects of a patient's life specifically related to physical and mental well-being. "Hard data" such as treadmill time in patients with heart failure may be of interest to clinicians, but is of little value to the patients. Frequently, "hard data" correlate poorly with the patient's actual functional status. An additional reason to add HRQL instruments to clinical outcomes measurements pertains to the phenomenon that patients with the same medical condition often respond differently to therapy. HRQL is a complementary method of meas-

uring the impact of therapy on chronic disease. Thus, HRQL might be used in tandem with explicit or implicit quality assurance review that is measuring the process of delivering care along with clinical outcome measures (e.g., blood pressure for hypertension or peak flow measures for asthma).[6]

Primary care providers, patients, and health care administrators are interested in HRQL outcomes because they are a method to measure the impact of therapy on the disease process. Hospital administrators and other policy makers have a high stake in these issues because payers are beginning to use HRQL data in their reimbursement policies.[16]

It is imperative that clinical pharmacists involved in providing primary patient care have a good working knowledge of HRQL instruments and are competent in choosing the appropriate methods to assess their interventions. Generic instruments and disease-specific instruments are the two general means by which HRQL can be measured.

The first modern health status questionnaires were very long, but their results were well validated. The Sickness Impact Profile (SIP) is an example of an early profile. It includes a physical dimension and a psychosocial dimension.[14–18] A dimension is a quality or aspect that is a component of health. The SIP also includes five independent categories including sleep, rest, eating, work, and home management, as well as recreation and pastimes. More recently, shorter profiles have been developed such as the Nottingham Health Profile and the Medical Outcomes Study (MOS) 36-Item Health Survey (SF-36) (Appendix 4).

The other approach in assessing HRQL is to focus on the aspects of health status that are specific to a particular area of interest or disease. By narrowing the area being observed, it is possible to gain increased responsiveness to changes in therapeutic interventions. Responsiveness relates to the instrument's ability to detect changes in the patient's status over time.[15–17] The instrument may be specific to a particular disease state (e.g., angina or arthritis), or to a population (e.g., the frail elderly), or to a physiologic problem (e.g., pain). In addition to responsiveness, these disease-specific instruments evaluate areas routinely addressed by primary care providers.[17]

Most generic and specific HRQL measures used today have been validated, but not in all populations. If an instrument is valid, it has been statistically determined to measure what it is intended to measure. Compendia of available measures, including critical reviews, can facilitate the choice of an instrument for a specific setting or purpose.[18] Appendix 4 contains some generic health profile instruments that can be used for various disease states, and, where possible, a disease-specific instrument was listed.

The Health Outcomes Institute has developed and validated several outcome instruments that can be used to evaluate patient outcomes following interventions by pharmacists.[19] These include hypertension/lipids, angina, asthma, chronic obstructive pulmonary disease, chronic sinusitis, hip replacement, hip fracture, depression, low back pain, osteoarthritis, alcohol abuse, stroke, rheumatoid arthritis, and prostatism (Appendix 4). The Health Outcomes Institute is located at 2001 Killebrew Drive, Suite 122, Bloomington, MN 55425; telephone (612) 858-9188.

Example

If pharmacists were providing primary care for hypertensive patients and wanted to compare the results of an intervention, they should first provide interventions based upon established therapeutic guidelines for treating hypertension such as those outlined by the Fifth Joint National Committee on Detection, Evaluation, and Treatment of Hypertension (JNC-V). With each patient encounter, they would collect the data in Appendix 2. These two procedures would ensure that the pharmacist is providing an appropriate process of care.

Prior to the intervention, the pharmacist would assess health outcome measures such as blood pressure, current medication adherence, and forms such as a general form (e.g., SF-36) and a disease-specific form (e.g., Hypertension/Lipid Form 5.1) (Appendix 4). After the pharmacist intervention, a predetermined period of time must elapse before these questionnaires can be repeated (e.g., 6–12 mo). The questionnaires and blood pressure assessments are then repeated and it is determined whether the intervention had any effect on the patient outcome.

Recommendations

1. When appropriate, generic assessment measures should be used to develop methods to evaluate overall patient outcomes after pharmacists' interventions. However, since these may not be the most appropriate techniques for specific pharmacotherapy interventions, disease-specific methods should also be considered.
2. Centers or individuals who want to evaluate patient outcomes that result from pharmacists' interventions should utilize instruments that have been developed and evaluated by experts.
3. When appropriate, patient outcomes after pharmacists' interventions and primary care activities should be assessed with disease-specific instruments that have been validated appropriately.

4. The choice of generic and/or disease-specific instrument(s), should be made by the multidisciplinary team when patient care is being assessed.

THE PROFESSIONAL RELATIONSHIP

Since primary care often involves an interdisciplinary team, many health care professionals provide care to the patient. Clinical pharmacists need to understand the legal implications of the care they provide, or of their patient interventions. Some of the medical-legal concepts that need to be addressed include: what establishes a professional relationship, how to terminate this relationship, abandonment, and harmful neglect. These issues are rooted in both tort and contract law. In actions of negligence, four legal elements must be addressed: duty, breach of this duty, damage, and causation.[20] In determining a pharmacist's duty, the central question is whether a particular conduct is a standard of pharmaceutical care. This is often quite controversial in that there may be certain activities, such as duty to warm, that are not accepted by all courts as a standard of care for pharmacists. If it is decided that the action is not a standard of care, the pharmacist cannot be held negligent. If it is, then the issues are whether the pharmacist breached that duty (standard of care), whether the patient was harmed (and to what extent), and whether the breach of duty caused the harm.

The essence of primary care is taking responsibility for the care of the patient to improve outcomes. Therefore, the following discussion is essential for the pharmacist–patient relationship in primary care.

Duty to Care

It is the pharmacist–patient relationship that gives rise to the pharmacist's duty to care.[21] The pharmacist–patient relationship usually involves an expressed or implied contractual agreement whereby the pharmacist offers to treat the patient with proper professional skill and the patient agrees to pay for such treatment. The pharmacist has the responsibility for practicing all facets of the profession competently. This could involve, for example, drug distribution, providing primary care, patient monitoring, patient and provider consultation/education, and other activities. As a result, the legal principles governing contract formation apply to the establishment of the pharmacist–patient relationship. At issue, however, is whether this contractual arrangement really exists between the pharmacist and the patient or whether it is between the pharmacist and some other entity such as the physician. The answer may depend on what the pharmacist is actually doing. If the pharmacist provides primary care functions, the contractual arrangement should be viewed as being with the patient.

Terminating the Relationship

If a pharmacist–patient relationship exists and it is to be terminated, the pharmacist must give the patient sufficient notice so that he may secure other professional care.[21] Even though the pharmacist's powers in terminating the relationship are limited, the patient has broad powers in terminating the relationship. The patient is free to unilaterally terminate the relationship at any time. From the moment the pharmacist is dismissed or discharged, he is relieved of all future professional responsibility to the patient.

Abandonment

Once established, the pharmacist–patient relationship imposes a duty of care upon the pharmacist that continues as long as attention is required, unless the pharmacist gives sufficient notice of termination or is discharged.[21] While this case law currently only applies to physicians, pharmacists who assume a caregiver role would also be subject to this duty. To recover on the theory of abandonment, the plaintiff must prove the following:

a) Existence of a pharmacist–patient relationship.
b) Unilateral severance by the pharmacist without reasonable notice and without providing an adequate substitute.
c) Necessity of continuing pharmaceutical attention.
d) Proximate cause.
e) Damages.

A pharmacist is immune from the abandonment charge when the patient voluntarily chooses not to return or discharges the pharmacist.

Abandonment may thus occur in two ways: through explicit withdrawal from a case or failure to attend the patient with due diligence. If the pharmacist fails to attend the patient with due diligence, he may also be liable under negligence principles. If he prematurely terminates the relationship despite the patient's continued need for care, he may also have abandoned the patient. The pharmacist has a definite right to withdraw from the case provided he gives the patient reasonable notice so that a patient may secure other attention. Failure by the patient to cooperate with the pharmacist may justify termination of the professional relationship by the pharmacist. The pharmacist is not justified in abandoning the patient unless the patient obstinately refuses treatment. Differences of

opinion on the factors surrounding a case may occur. Therefore, it would be prudent for the pharmacist to document carefully events and to offer to obtain a substitute clinician for the patient, and even then alternative care arrangements must be made.

Harmful Neglect

Decisions concerning frequency of patient visits are an important medical-legal issue. Pharmacists can be held liable for harmful neglect, an act of negligence involving nondiligent care of the patient. Courts have ruled, "A physician is not chargeable with neglect on account of the intervals elapsing between visits, where the injury requires no attention during the intervals, but is negligent where attention is required."[22]

The establishment for "proximate" or "legal" causation is the first step.[23] A factual link between the pharmacist's conduct and the patient's injury and whether the pharmacist could have foreseen the harm must be determined. The plaintiff must compare what did occur with what would have occurred if contrary-to-fact conditions existed. As an example, in a case involving a pharmacist, if the pharmacist had provided more frequent visits, would a more favorable outcome have resulted? The plaintiff would have to prove, by a preponderance of the evidence, that the infrequency of visits was the cause of damages to him. In addition, even if it is established that the pharmacist's conduct caused the patient's injury, a question of forseeability may be raised. In general, unless the pharmacist could have foreseen that harm would occur, there will be no liability. The issue of foreseeability would most likely be part of the determination of duty. Many of the consensus statements and guidelines included in this paper describe appropriate intervals of follow up that, if followed, might reduce the liability of clinical pharmacists.

The jury would be instructed not to consider a pharmacist's workload as a legitimate determination of frequency of follow-up care. Pharmacists should be aware that having more patients than time allows does not relieve them of their responsibility to provide proper follow-up care.

Pharmacists do not carry the sole burden of what happens to their patients during intervals between appointments. Patients also have responsibilities with regard to the management of their illnesses. The Supreme Court of Maine ruled "it is the duty of a patient to follow the reasonable instructions and submit to the reasonable treatment prescribed by his physician or surgeon."[24] If the patient fails in his duty and his conduct directly contributes to the injury, he may be precluded from or limited in seeking damages. Some state laws provide for contributory negligence where any negligence by the plaintiff completely bans recovery. Other states have comparative negligence where blame is essentially apportioned between the plaintiff and defendant.

In summary, pharmacists' decisions regarding follow-up care are subject to legal scrutiny. As standard guidelines concerning the appropriate frequency of follow-up visits for outpatient management of most diseases are not routinely available, clinicians are vulnerable to actions for harmful neglect. Lacking such standards, a jury of laypersons listens to "expert testimony" and decides whether appropriate care was given. Busy workloads of pharmacists who service a large number of patients are not considered a defense against harmful neglect. If a practitioner cannot provide adequate care to each patient, an equally competent substitute must be named. Finally, it is essential to remember that the patient has obligations in the management of his own health. To document appropriate pharmacists' advice to patients, written instructions should be provided that clearly and specifically outline what the patient should do during intervals between visits, and full and appropriate records of patient visits must be maintained.

SUMMARY

This Task Force report is designed to provide administrators and pharmacy practitioners with recommendations that assist them in establishing and evaluating pharmacy services and assessing patient outcomes in ambulatory/primary care. Each setting will have unique features requiring specific processes be tailored to that institution or clinic. By utilizing the outcome instruments, practice guidelines, and other materials listed in this report, the clinician should be able to establish a valuable practice in most primary care settings.

ACKNOWLEDGMENTS

This article was written in collaboration with Joseph L. Fink III, JD, and Francis B. Palumbo, PhD, JD, who assisted with the legal discussions and Kathleen M. Bungay, PharmD, and Eleanor Perfetto, PhD, who provided significant guidance and advice with the health care process and outcomes sections.

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Appendix 1 Application for scope of practice

Clinical Pharmacy Specialists

Name: _____
Position on hospital staff: _____
Pharmacy school(s): _____
Date(s) of graduation: _____
Graduate degree: _____
Graduation: _____
Board certified in pharmacotherapy?: Yes____ No____
Board certified in other pharmacy specialty?: Yes____ No____ NA____
Specialty area: _____
States currently licensed: _____

The following are the clinical scope of practices granted to you as a member of the staff of the _____ Hospital (Clinic), located in _____ (city), _____ (state). These determinations were made through a thorough review of your education, training, and experience, and demonstrated competence by the Professional Standards Board and approved by the Director. If you change positions and/or if your duties change (i.e., a geriatric clinical pharmacist moves to medical oncology), then you must reapply for practices specific to that area.

Areas of Practice:

A = Ambulatory Care

A. Routine duties: Routine duties are defined as those duties that are performed on a regular, repetitive basis.

(1) Category A-1: Routine duties that require review by the physician supervisor who will note concurrence or addendum as indicated. Countersignature of the medical record is required within 24 hours.

	Requested
• taking and recording verbal orders from physicians	A

(2) Category A-2: Routine duties that do not require review by the physician supervisor unless so indicated. These duties will be reviewed by the physician supervisor on a regular basis through a random sampling process. Results of this review will be discussed with the clinical pharmacist as appropriate.

	Requested
• provision of formal written consultations upon request in the areas of pharmacotherapy and pharmacokinetics	A
• provision of written initial assessments in the progress notes	A
• provision of follow-up notes within the progress notes	A
• taking medication/therapeutic histories	A
• measuring vital signs and performing physical examinations of relevant organ systems for the purpose of monitoring drug therapy	A
• collecting laboratory specimens (i.e., drawing blood)	A
• order the following noninvasive tests:	
(a) laboratory tests (e.g., PT, CBC)	A
(b) EKGs	A
(c) Holter monitors	A
(d) PFTs	A
(e) echocardiograms	A
(f) x-rays (e.g., CXR)	A
• order appropriate consultations from the following services:	
(a) dental	A
(b) dietetics	A
(c) medical specialties	A
(d) psychiatry	A
(e) psychology	A
(f) radiology	A
(g) social work	A
(h) surgical specialties (old problems)	A

(*Continued*)

Appendix 1 Application for scope of practice (*Continued*)

B. Non-Routine/Non-Emergency Duties:

	Requested	
• authority to write prescriptions for medication refills for medical problems that are stable in patients followed in outpatient clinics. The clinical pharmacist is not authorized to write prescriptions that are used to initiate any form of drug therapy.	A	
• authority to make adjustments in dosage as clinically indicated for a period of up to 3 months between physician visits using the following classes of drugs:		
1. antihistamine drugs	A	
2. antiinfective agents	A	
3. antineoplastic agents		(indicates not applicable to this ambulatory care pharmacist)
4. autonomic drugs	A	
5. blood formation and coagulation	A	
6. cardiovascular drugs	A	
7. central nervous system agents	A	
8. gastrointestinal drugs	A	
9. hormones and synthetic substitutes	A	
10. respiratory smooth muscle relaxants	A	
• limited authorization to approve the use of restricted or nonformulary medications when the use of such agents is within the established guidelines or approved criteria for use at this facility (i.e., antibiotics, chemotherapy)	A	

C. Emergency Duties: Carried out for patients in life-threatening situations where a physician is not immediately available. The clinical pharmacist initiates this activity but makes every effort to summon a physician as soon as possible (i.e., cardiopulmonary resuscitation, and, if advanced cardiac life support-certified, electrodefibrillation).

D. Miscellaneous Duties: Those duties that do not fall into the first category.

• conduct clinical research protocols A

I do hereby request the above outlined scope of practices. I have read and agree to abide by the bylaws of the _____ Hospital.

Signature of applicant _____ Date _____

Signature of physician supervisor _____ Date _____

Chief, Pharmacy Service _____ Date _____

Chief of Staff _____ Date _____

Director _____ Date _____

Appendix 2 Evaluating process of care: Example quality assurance in primary care

Medical Records will be reviewed on a quarterly basis. Twenty-five charts will be randomly selected and reviewed for the following items:

1. Progress notes written in an appropriate S.O.A.P. format.
2. Determine if the subjective and objective information is consistent with the assessment and plan.
3. Past medical history and family history is obtained at least once for each patient.
4. Social, diet, and exercise history is recorded at least every 4 months.
5. Medication history recorded at least once.
6. Current prescription and nonprescription medication recorded on each visit.
7. Compliance is assessed on each visit.
8. Each visit contains thorough questioning concerning disease control, signs or symptoms of disease progression or new complications, and signs or symptoms of adverse reactions.
9. Each visit documents appropriate objective information such as laboratory, physical assessment data, vital signs, etc.
10. All patient counseling concerning drug therapy, compliance, diet, exercise, and other lifestyle factors are recorded.

(*Continued*)

Appendix 2 Evaluating process of care: Example quality assurance in primary care *(Continued)*

11. Therapeutic goals are clearly stated.
12. Appropriate recommendations and drug regimen changes are made and documented in the plan.
13. Documentation of any actions that are beyond the scope of practice that were authorized by a physician.
14. Appropriate timing of follow-up visit is included in every plan.

Appendix 3 Treatment guidelines and review articles

Hypertension guidelines

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Hyperlipidemia guidelines

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Disease-specific tools to measure outcomes

Hypertension outcomes

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Professional Associations, Clinical Pharmacy Careers in

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INTRODUCTION

A career in a professional association can be an extremely rewarding way to practice clinical pharmacy while serving the members of the profession. Positions may focus on many different programmatic areas (Table 1). In addition to positions in national associations, pharmacists serve important roles in state and regional associations. There are also many related biomedical associations in which pharmacists may be employed.

TYPES OF POSITIONS AVAILABLE

Many types of positions are possible within associations. Those working for large pharmacy associations may have more than 100 coworkers. Employees of large associations typically have fairly narrow responsibilities and focus. Within smaller associations, with staffs of 40 or less, areas of responsibility are broad, and many positions are combined or do not exist.

Approximately 20 of the 100 employees of the American Pharmaceutical Association are pharmacists. Of 20 employees of the Academy of Managed Care Pharmacy, 4 are pharmacists. The American College of Clinical Pharmacy, with a staff of 30, employs 6 who are pharmacists. The American Society of Health-System Pharmacists, with a staff of approximately 175 persons, has a larger proportion who are pharmacists due to their extensive publishing efforts.

Clinical pharmacists within associations are most frequently employed within areas where their backgrounds are of most benefit. Some of these areas include serving as the chief executive officer, working with chapter relations, education, government and professional affairs, marketing, membership, and publications, including the journals of the association.

Depending on the size of the association staff, clinical pharmacists may start out working with specific publications, membership and chapter activities, or educational program planning. As they gain experience and familiarity with their roles, they may take on greater managerial roles and broader areas of responsibility. Those with the greatest experience and expertise may move into director, or vice presidential, positions, or even become the chief executive officer for the association.

According to the American Society of Association Executives (ASAE), the average total compensation for association executives in 1996 ranged from $48,000 to $117,000.[1] Compensation has increased over the last few years by percentages greater than business averages (5–10% for many positions). Many associations use ASAE survey information, faculty and deans' salary data collected by the American Associations of Colleges of Pharmacy,[2] and salary data from other segments of the profession (e.g., managed care pharmacists, industry pharmacists) as benchmarks for pharmacist executive staff salaries.

Regardless of the association's scope or focus, pharmacists must be responsive to the needs and desires of the membership served. Each association employee is ultimately responsible to the members and prospective members for whom the association exists. The membership at large is generally represented by an elected governing board (Board of Directors, Board of Regents, Board of Trustees), and sometimes a house of delegates. Typically, the activities of the association are guided through a strategic planning process, which sets the direction for the association for the next few years.

CAREER PATHS AND PREPARATION

Several paths exist for entry into a career with a professional association. Many association executives have had an earlier career as a practicing member of their profession. They have worked "in the trenches" for a

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006264

Table 1 Programmatic and management positions within professional associations

Position title(s)	Major responsibilities	Examples of primary focus
Association Foundation Executive, Director of Research Institute	Leads the not-for-profit, charitable arm of the association.	Research training and grants programs; professionwide research; fund-raising.
Attorney	Legal counsel for association.	Resource for staff, board, and officers in matters of nonprofit or antitrust law; personnel and copyright issues; legal disputes.
Chapter Relations, Manager of	Primary association liaison with chapters.	Programs and services for chapters and other affiliates.
Chief Executive Officer, Executive Director, Executive Vice President	Oversees all aspects of the association; reports to the elected governance of the association.	Strategic direction; "the big picture."
Computer/Management Information Systems, Manager of	Computer support systems.	Database development; membership database management; web site development and maintenance.
Deputy Chief Executive, Associate Executive Director	Responsible for major projects; often works with personnel issues.	Specific projects of importance to the association.
Education, Director/Vice President or Manager	Development and delivery of educational programming, including certificate programs and other training programs.	Scientific abstracts; meeting standards for continuing pharmaceutical education; development of program content; working with speakers; delivery of live, printed, and online programming; educational grants.
Finance, Director of/Controller	Oversees financial management of the association.	Accounting; management of short-, intermediate-, and long-term investments; financial reporting to chief executive officer and governing board.
Government Relations (often paired with Professional Affairs), Director/Vice President of	Leads association's advocacy efforts to government, legislative, and regulatory bodies.	Lobbying; tracking legislative initiatives to alert membership of important issues; writing suggested legislation; interaction with representatives of government bodies.
Human Resources, Manager of	Personnel management.	Hiring and firing; employee policies; employee benefits.
Marketing, Director/Vice President or Manager	Promotion of the association.	Promotion of membership, meetings, publications.
Meetings and Expositions, Director/Vice President or Manager	Planning for conventions of the association.	Meeting logistics; site selection; audiovisual requirements; exhibits program; vendor contracts.
Member Services, Director/Vice President or Manager	Membership recruitment and retention.	Dues notices; recruitment of new members; services for members; promotional materials; member complaints.
Professional Affairs (often paired with Government Relations), Director/Vice President	Primary contact with other professional associations.	Development of professional policies; attends meetings of other related associations; offers comment on behalf of association regarding position statements of other associations; collaboration with other associations regarding mutual interests.

(Continued)

Table 1 Programmatic and management positions within professional associations (*Continued*)

Position title(s)	Major responsibilities	Examples of primary focus
Public Relations Director/ Vice President or Manager	Image of the association to the rest of the world.	Press releases; quotations for publication; "official voice" of the association.
Publications Director/Vice President or Manager/Editor	Printed and online publications to meet needs of membership.	Official journal; books; home study programs; newsletters.

number of years, and were active in the association as a volunteer, through committee work, attendance at meetings, presentation of scientific abstracts, or elected office. By becoming known as a reliable volunteer, they set the stage for movement into association employment. This path is advantageous in providing the association with an employee whom they know and who understands the membership and the profession. However, a disadvantage of this path is that clinical pharmacists have rarely received the management training and experience necessary for association work.

Others who identify association work as their career objective early in their training may enter this type of work through summer internships, experiential clerkships and externships, and executive residencies, or by accepting their first postgraduate job with an association and then advancing though various positions and departments. Many of these opportunities are listed in a document prepared by the member organizations of the Interorganizational Council on Student Affairs.[3]

Regardless of the career path chosen, preparation for a career in association management should ideally include several elements. Exposure to association work can be obtained through an internship, a clerkship, or an executive residency. These experiential activities provide excellent opportunities for exposure to what it might be like to work for an association.

Experience as a practicing member of the profession can be an excellent way to prepare for association work. Through spending time in actual patient care, research, and teaching, prospective association pharmacists can learn firsthand what members do and what their struggles are. Furthermore, by becoming involved with associations on a volunteer basis, it is possible to experience how the association works. Volunteering also provides an opportunity to showcase an applicant's talents and dependability to the association. Choosing to work for employers who will allow time and support for association work is also beneficial.

Other areas of preparation that are very helpful involve skills aside from those taught in traditional pharmacy curricula. Those thinking of careers in associations should keep their eyes open to issues and events, the actions of other related groups, and the opinions of colleagues. They need to pay attention to the business and the politics of the profession and be informed about them.

Finally, training in how to manage projects, people, and finances can be very helpful for association managers. Many of the skills necessary to be an excellent clinical pharmacist are opposite those required to be an excellent manager. Training and experience in this area are crucial to excelling in an association career.

BENEFITS OF ASSOCIATION WORK

There are many benefits of association work. Working within an association provides increased opportunities to be involved with the discipline of clinical pharmacy. For someone who has practiced patient care, conducted research, or taught, this can provide an exciting new direction with new challenges and new skills to learn. Those who have been members of the association before working for it often appreciate the opportunity to work for a group having a mission they believe in and from which they have benefited as a member.

Association work necessarily involves communication with its members. Those working in this field have many more acquaintances among their peers and with representatives of the pharmaceutical industry. Establishing and maintaining contacts is an important part of this work. Those who enjoy interacting with people will especially enjoy this aspect of association life.

A clinical career within an association can be an opportunity for continued learning and professional growth. Association managers often need to enhance their skills in business management, public relations, marketing, project management, advocacy, politics, personnel management, legal issues, and many other areas, depending on the scope of their responsibilities. Adopting the attitude of a lifelong learner is essential, as the profession and the world change rapidly. It is necessary to constantly

learn new knowledge and skills to keep up with these rapid changes.

Working for an association opens many career opportunities in related fields, with other associations, with the pharmaceutical industry, in other management jobs, and in private consulting. The skills gained through association work are widely transferable to other professions, as well as back to clinical practice.

Clinical pharmacists within associations have many opportunities to work on new projects pertaining to the membership and the profession. They can be creative not only in developing a project, but also in funding, implementing, and promoting it. Association work provides a wide variety of opportunities to practice clinical pharmacy in ways that, although different from traditional roles, affect patient care and the profession.

Many of the knowledge and skills taught in clinical pharmacy curricula are applicable to association work. For example, those working with educational programs often draw on their pharmacy backgrounds to help members design better educational offerings. Also, research techniques learned in academic training are applicable to association research.

Perhaps the greatest benefit of association work is the ability to represent the association's members, seeking to improve their practices and opportunities, and to make a difference in the profession.

CHALLENGES OF ASSOCIATION WORK

Those choosing to practice clinically within a professional association must have excellent organizational and time management skills. They will experience many pressures from various directions and must be skilled at prioritizing their activities. Excellent written and verbal communications skills are also essential.

Association executives must find a balance between being a member of the association and serving on the staff. An attitude of servanthood is absolutely essential. It is also critical to find a balance between listening to members and responding to their needs versus taking the lead and establishing the direction of the association. The most responsive associations are typically "member driven," meaning that the association staff take their lead from the elected officers of the organization, with a focus on implementing, rather than establishing policy.

When working with speakers, authors, and committees, who by definition are performing volunteer work, association executives must be prepared to help members meet their deadlines, through reminders, clear communication, and advance planning. Missed deadlines by members have the potential to result in periods of great stress for association staff who in turn have printing or other deadlines that cannot be changed. As this can be a source of great stress, it is essential to have the personal fortitude to deal with the unexpected and uncontrollable.

Because associations must function as businesses, serving as stewards of their members' resources, there is less freedom for association employees to function as independently as they might in an academic environment. Budgets must be developed and adhered to, and performance targets established and met. Also, because the elected officers change regularly, the direction of the association and the style of the governing board can change frequently. Clinical pharmacists working within associations must be flexible, as issues and responses can change, may not always agree with their personal opinions, and are often outside their control.

CONCLUSION

Working as a pharmacist within a professional association is a challenging, yet rewarding way to practice clinical pharmacy. This career choice should be strongly considered by those who seek to serve their colleagues and the profession by helping them manage and adapt to ever-changing issues in clinical pharmacy.

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Psychiatric Pharmacy Specialty Practice

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INTRODUCTION

Psychiatric pharmacy practice is a rewarding specialty with diverse opportunities to have an impact on the care of patients directly through innovative practice models, quality assurance, and patient education, and indirectly through professional education, the development of treatment guidelines, clinical research, and careers in the pharmaceutical industry.[1–3]

Psychiatric illness occurs in 50% of the population over the course of a lifetime and nearly 30% over the course of a year.[4] It affects all age groups and causes significant morbidity, mortality, and diminished quality of life.[4,5] Medication management is essential to treat acute symptoms of psychiatric illness and to prevent relapse. In fact, psychotropic drugs (antidepressants, antipsychotics, anxiolytics, hypnotics mood stabilizers, stimulants) comprised 10% of the top 200 brand name and generic drugs dispensed from retail pharmacies in the year 2001.[6]

Similar to other specialty practice areas, psychiatric pharmacy requires core knowledge of disease state management and the ability to demonstrate clinical skills in applying knowledge to improve patient care. A distinguishing aspect of psychiatric pharmacy is the requirement that the practitioner have an interest and aptitude for interpersonal communication and developing professional relationships. Patient evaluation and drug therapy assessment is based on an interview that uses mental status examination, as well as standardized psychiatric rating scales, to assess symptoms and adverse effects. Clinical service involves collaboration with physicians, nurses, social workers, psychologists, and other health care professionals.[1,3]

A specialized residency is ideal to prepare a pharmacist for a career in psychiatric pharmacy practice. There are approximately 25 to 30 1-year, post-PharmD residencies in psychiatric pharmacy practice across the United States, with 17 receiving accreditation by the American Society of Health-System Pharmacists (ASHP).[7,8] Each residency may offer a unique feature such as an ambulatory care focus or teaching skills development; however, the emphasis of residency training is on specialized clinical knowledge and skill development.[9]

Given the high prevalence of psychiatric illness and specialized expertise required for successful pharmacy practice, it makes sense that psychiatric pharmacy has become one of the five specialty practice areas certified by the U.S. Board of Pharmaceutical Specialties. As of December 2001, there were 387 certified psychiatric pharmacy specialists.[10] The certification process started in 1990, when a coalition of educators and practitioners identified a need to define the specialized knowledge and skills required to function as a competent psychiatric pharmacy specialist.[2] The coalition's petition was sponsored by the ASHP and the first examination took place in December 1996.

This article presents opportunities in psychiatric pharmacy, provides examples of model practice settings, discusses the impact of psychiatric pharmacy on health outcomes, reviews the tools used by specialty practitioners, and discusses networking opportunities in psychiatric pharmacy specialty practice.

OPPORTUNITIES IN PSYCHIATRIC PHARMACY

Opportunities in psychiatric pharmacy continue to expand with specialists practicing in hospitals, clinics, long-term care facilities, developmentally disabled centers, prisons, academia, and the pharmaceutical industry.[1,3] Although acute care facilities exist to treat the most severely ill patients, primary care clinics provide service for the majority of patients. Model practice settings exist for both acute and primary care, and are discussed later in this article. Other opportunities are discussed in this section.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006238

It is estimated that 25–50% of patients in long-term care facilities suffer from neuropsychiatric disorders that are functionally impairing.[11] At least 26% of incarcerated adults[12] and 52% of children in the juvenile justice system meet criteria for a DSM-IV-TR disorder.[13] When substance abuse/dependency is included in the adult population, the incidence rises to 71%.[12] Psychiatric pharmacist specialists can provide consultation on optimizing drug therapy for patients in these settings.

Half of the homeless suffer from mental illness, and rely on community outreach, missions, and government-run clinics to provide service.[14,15] A psychiatric pharmacist is uniquely qualified to manage the coordination of medication follow-up for these patients. Developmentally disabled individuals are often treated for a combination of neurologic and psychiatric problems and, therefore, have unique drug interaction considerations and communication obstacles. Psychiatric pharmacists currently serve as consultants and members of multidisciplinary treatment teams to optimize the care of these individuals.[3,16]

Quality of care for individuals with psychiatric illness has come under scrutiny with several studies documenting a need for improvement in medication management.[17–19] Psychiatric pharmacists have the opportunity to improve care through quality assurance surveys/drug-use evaluations, patient and staff education,[3,20] and direct medication management.[1] Psychiatric pharmacist specialists are an important community resource for consumer advocacy groups such as NAMI, also known as the National Alliance for the Mentally Ill.[21]

In addition, psychiatric pharmacists have opportunities for involvement in treatment guideline development for psychiatric disorders. The American Pharmaceutical Association recruited psychiatric pharmacy specialists to develop their guidelines for psychiatric disease state management.[22]

Dr. Lynn Crismon's work in developing the Texas Medication Algorithms for treatment of depression in children and adults and the treatment of attention-deficit hyperactivity disorder in children[2,23,24] laid the groundwork for psychiatric pharmacists to work with psychiatrists, psychologists, other health care professionals, and consumer groups to develop and implement national therapeutic guidelines.

MODEL PRACTICE SETTINGS

An attractive feature of psychiatric pharmacy is that it offers creativity in developing a practice that is individualized to the setting and patient population of interest to the practitioner. Model practice settings in hospitals and several clinics are discussed in the following paragraphs.

Hospital

Psychiatric pharmacy specialists in hospitals provide a wide range of services, including participation in multidisciplinary treatment planning, medication education groups for patients, therapeutic drug monitoring, discharge counseling, and quality assurance.[3,20] Model practices exist across the United States for the acute care psychiatric pharmacist; however, the scope of practice is variable based on staffing, institutional support, and interest of the practitioner. Through the years, a patient-focused model has evolved using the principles of pharmaceutical care whereby the pharmacist develops a professional relationship with the patient in addition to staff and takes responsibility for health outcomes.

Psychiatric pharmacy in the acute care setting involves patient interviews for initial assessment and follow-up monitoring. The pharmacist obtains a medication history to facilitate treatment plan development, in addition to participating in multidisciplinary rounds for exchange of information and therapeutic decision making. The inpatient psychiatric pharmacist conducts therapeutic drug-level monitoring of lithium and anticonvulsants. Conducting medication education groups and individual medication counseling sessions are standard functions of the inpatient psychiatric pharmacist.[25]

Primary Care

In the primary care setting, there are several practice models for pharmacy-run clinics. Typically, patients are evaluated by a psychiatrist and referred to the psychiatric pharmacist for medication management and ongoing assessment.[26] The Veteran's Administration (VA) health care system was one of the first to use psychiatric pharmacy specialists in mental hygiene clinics in the 1970s. Currently, the VA health care system supports psychiatric pharmacist specialist involvement in several psychiatric clinics, including the cognitive disorders, mood disorders, psychiatry emergency, geropsychiatry, and clozapine clinics.[27,28]

Extent of involvement varies across VA systems. For example, at the VA clinic in La Jolla, California, a psychiatric pharmacist's scope of practice includes: 1) assessing clinical response to medication via mental status exam and psychiatric interviewing techniques; 2) assessing development of adverse drug reactions; 3) ordering and evaluating appropriate laboratory tests to assess cli-

nical response, assess development of adverse drug reactions, and evaluate therapeutic drug levels; 4) making changes in psychotropic drug therapy using the physician order form or through direct order entry into the computer; 5) assessing patient compliance with medications by analyzing computer dispensing records and quantities of medications dispensed versus doses remaining; 6) documenting findings, actions, and plans in the patient's medical records on the progress notes form or through direct progress note entry into the computer; 7) providing prescriptions for all medications with enough medications to last until the patients' next appointment; 8) providing patient medication education, including methods of coping with certain side effects, recognizing symptoms of toxicity, and emphasizing the importance of compliance, and when appropriate, providing written information; and 9) rescheduling patients for follow-up appointments with an appropriate clinician. In a VA clinic in Waco, TX, a psychiatric pharmacist specialist has similar scope of practice but is assessed quarterly, in writing, by the supervising psychiatrist.

Scott and White hospital in Texas is an example of a pharmacy-run women's health clinic. In this model, the obstetrics-gynecology physician or nurse identifies patients at risk for mood disorders, including premenstrual syndrome and premenstrual dysphoric disorder, and refers them to the pharmacist for further evaluation, treatment, and drug therapy monitoring. Patient approval ratings were 96% excellent.[29]

Industry

Psychiatric pharmacy specialists are vigorously recruited by industry to serve as medical science liaisons, neuroscience managers, members of advisory boards, and resources of drug information for physicians and other health care professionals.[1]

BENEFITS OF SPECIALTY PRACTICE

Several U.S. studies report improved care, improved level of functioning, and economic savings attributed to psychiatric pharmacist interventions;[3] however, the studies are small, generally retrospective in nature, and most lack rigorous controls. One chart review of 60 clinic patients compared pharmacist prescribing with psychiatrist prescribing and determined pharmacist prescribing was as good as or better than physician prescribing.[26] The largest study was a chart review in some 4700 patients, which documented that 66% of pharmacist recommendations were implemented with an extrapolated cost savings based on decreased clinic visits and decreased prescriptions of $22,241.25 over 3 months.[30]

One prospective study from Australia analyzed clinical pharmacy interventions on an inpatient psychiatric unit over a 6-month period. Two hundred and four interventions were proposed for 69 patients, 91.7% of which were accepted. Some of the interventions (20.3%) were estimated to be of major clinical significance, with added cost savings of 24,700 based on cutting 38 days of inpatient care at $650/day.[31]

TOOLS

Psychotropic drug therapy expertise, interview technique, and the mental status exam are the most used tools of the psychiatric pharmacist. Validated psychiatric rating scales are also used and allow objective measurement of drug therapy outcomes. Psychiatric pharmacists develop expertise in using standardized rating scales such as the Hamilton-Depression Rating Scale and the Monitoring of Side Effects Scale (OSES).[32,33] American Psychiatric Association rating scales and online references, such as *Clinical Pharmacology*,[34] are available on CD-rom and make the information easily retrievable in settings with computer capabilities. Clinical psychiatric pharmacists use portable laptop or notebook computers and personal data assistants, or PDAs, to keep track of patient profiles, drug therapy recommendations, and outcomes.

NETWORKING

Networking can be accomplished by participating in national meetings where psychiatric pharmacy specialists gather to exchange ideas, participate in neuropsychiatric educational programming, and discuss professional issues such as residency training, reimbursement, and health care policy. These national meetings include the College of Psychiatric and Neurologic Pharmacists,[8] ASHP's Section of Clinical Specialists in Psychiatric and Neurologic Pharmacy,[7] and the American College of Clinical Pharmacy's (ACCP's) central nervous system practice-related network.[35] The "psypharm" listserv has approximately 400 participants (George Foose, personal communication) and is an effective tool for "rapid-response" networking with national and international psychiatric pharmacists. To become a member of psypharm and/or of the College of Psychiatric and Neurologic Pharmacists (CPNP) listserv, log on to the CPNP web site or contact Dr. George Foose via e-mail at gfoose@msn.com.[8,36]

INTERNATIONAL

Psychiatric pharmacy is an internationally recognized specialty, with organized representation in Canada, the United Kingdom, Scotland, and the Netherlands. The United Kingdom Psychiatric Pharmacy Group has its own web site,[37] and offers a postgraduate certificate in psychiatric pharmacy for practitioners in Great Britain and other countries. Currently, certification is ongoing for practitioners in Hong Kong, Canada, and New Zealand. The Scottish organization is known as The Scottish Pharmacists in Mental Health. The Dutch Association of Hospital Pharmacists has a special interest group in the field of psychiatry, with goals to elevate psychiatric pharmacy practice to include pharmaceutical care and therapeutic drug monitoring, in addition to distributive services. Practitioners from the United Kingdom and Canada report practice activities that are similar to U.S. psychiatric pharmacists with regard to multidisciplinary treatment planning, patient and staff education, and quality assurance.

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