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# BASIC & CLINICAL PHARMACOLOGY

The First Full PDF Copy By Dr Murtadha Al-Shareifi

12th Edition

Mc  
Graw  
Hill

**LANGE**<sup>TM</sup>



# SCHEDULE OF CONTROLLED DRUGS<sup>1</sup>

## SCHEDULE I

(All nonresearch use illegal under federal law.)

### Flunitrazepam (Rohypnol)

#### Narcotics:

Heroin and many nonmarketed synthetic narcotics

#### Hallucinogens:

LSD

MDA, STP, DMT, DET, mescaline, peyote, bufotenine, ibogaine, psilocybin, phencyclidine (PCP; veterinary drug only)

#### Marijuana

#### Methaqualone

## SCHEDULE II

(No telephone prescriptions, no refills.)<sup>2</sup>

#### Opioids:

Opium

Opium alkaloids and derived phenanthrene alkaloids: codeine, morphine, (Avinza, Kadian, MSContin, Roxanol), hydromorphone (Dilaudid), oxymorphone (, Exalgo), oxycodone (dihydrocodeine, a component of Oxycontin, Percodan, Percocet, Roxicodone, Tylox)

Designated synthetic drugs: meperidine (Demerol), methadone, levorphanol (Levo-Dromoran), fentanyl (Duragesic, Actiq, Fentora), alfentanil (Alfenta), sufentanil (Sufenta), remifentanyl (Ultiva), tapentadol (Nycynta)

#### Stimulants:

Coca leaves and cocaine

Amphetamine

Amphetamine complex (Biphetamine)

Amphetamine salts (Adderall)

Dextroamphetamine (Dexedrine, Procentra)

Lisdexamfetamine (Vyvanse)

Methamphetamine (Desoxyn)

Methylphenidate (Ritalin, Concerta, Methylin, Daytrana, Medadate)

Above in mixtures with other controlled or uncontrolled drugs

#### Cannabinoids:

Nabilone (Cesamet)

#### Depressants:

Amobarbital (Amytal)

Pentobarbital (Nembutal)

Secobarbital (Seconal)

## SCHEDULE III

(Prescription must be rewritten after 6 months or five refills.)

#### Opioids:

Buprenorphine (Buprenex, Subutex)

Mixture of above Buprenorphine and Naloxone (Suboxone)

The following opioids in combination with one or more active non-opioid ingredients, provided the amount does not exceed that shown:

Codeine and dihydrocodeine: not to exceed 1800 mg/dL or 90 mg/tablet or other dosage unit

Dihydrocodeinone (hydrocodone in Hycodan, Vicodin, and Lortab): not to exceed 300 mg/dL or 15 mg/tablet

Opium: 500 mg/dL or 25 mg/5 mL or other dosage unit (paregoric)

#### Stimulants:

Benzphetamine (Didrex)

Phendimetrazine (Bontril)

#### Depressants:

Schedule II barbiturates in mixtures with noncontrolled drugs or in suppository dosage form

Butabarbital (Butisol)

Ketamine (Ketalar)

#### Cannabinoids:

Dronabinol (Marinol)

#### Anabolic Steroids:

Fluoxymesterone (Androxy)

Methyltestosterone (Android, Testred, Methitest)

Nandrolone decanoate (Deca-Durabolin) Non US

Nandrolone phenpropionate (Durabolin) Non US

Oxandrolone (Oxandrin), Oxymetholone (Androl-50)

Stanozolol (Winstrol),

Testolactone (Teslac),

Testosterone and its esters

## SCHEDULE IV

(Prescription must be rewritten after 6 months or five refills; differs from Schedule III in penalties for illegal possession.)

#### Opioids:

Butorphanol (Stadol)

Difenoxin 1 mg + atropine 25 mcg (Motofen)

Pentazocine (Talwin)

#### Stimulants:

Armodafinil (Nuvigil)

Diethylpropion (Tenuate) not in US

Modafinil (Provigil)

Phentermine (Ionamin, Adipex-P)

#### Depressants:

Benzodiazepines

Alprazolam (Xanax)

Chlordiazepoxide (Librium)

Clonazepam (Klonopin)

Clorazepate (Tranxene)

Diazepam (Valium)

Estazolam (ProSom)

Flurazepam (Dalmane)

Halazepam (Paxipam)

Lorazepam (Ativan)

Midazolam (Versed)

Oxazepam (Serax)

Prazepam (Centrax)

Quazepam (Doral)

Temazepam (Restoril)

Triazolam (Halcion)

Chloral hydrate (Somnote)

Eszopiclone (Lunesta)

Meprobamate (Equanil, Miltown, etc)

Methobarbital (Mebaral)

Methohexital (Brevital)

Paraldehyde

Phenobarbital

Zaleplon (Sonata)

Zolpidem (Ambien)

## SCHEDULE V

(As any other nonopioid prescription drug)

Codeine: 200 mg/100 mL

Difenoxin preparations: 0.5 mg + 25 mcg atropine

Dihydrocodeine preparations: 10 mg/100 mL

Diphenoxylate (not more than 2.5 mg and not less than 0.025 mg of atropine per dosage unit, as in Lomotil)

Ethylmorphine preparations: 100 mg/100 mL

Opium preparations: 100 mg/100 mL

Pregabalin (Lyrica)

Pyrovalerone (Centroton, Thymergix)

<sup>1</sup>See <http://www.usdoj.gov/dea/pubs/scheduling.html> for additional details.

<sup>2</sup>Emergency prescriptions may be telephoned if followed within 7 days by a valid written prescription annotated to indicate that it was previously placed by telephone.

a LANGE medical book

# Basic & Clinical Pharmacology

Twelfth Edition

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# Preface

The twelfth edition of *Basic & Clinical Pharmacology* continues the important changes inaugurated in the eleventh edition, with extensive use of full-color illustrations and expanded coverage of transporters, pharmacogenomics, and new drugs. Case studies have been added to several chapters and answers to questions posed in the case studies now appear at the end of each chapter. As in prior editions, the book is designed to provide a comprehensive, authoritative, and readable pharmacology textbook for students in the health sciences. Frequent revision is necessary to keep pace with the rapid changes in pharmacology and therapeutics; the 2–3 year revision cycle of the printed text is among the shortest in the field and the availability of an online version provides even greater currency. In addition to the full-color illustrations, other new features have been introduced. The Case Study Answer section at the end of chapters will make the learning process even more interesting and efficient. The book also offers special features that make it a useful reference for house officers and practicing clinicians.

Information is organized according to the sequence used in many pharmacology courses and in integrated curricula: basic principles; autonomic drugs; cardiovascular-renal drugs; drugs with important actions on smooth muscle; central nervous system drugs; drugs used to treat inflammation, gout, and diseases of the blood; endocrine drugs; chemotherapeutic drugs; toxicology; and special topics. This sequence builds new information on a foundation of information already assimilated. For example, early presentation of autonomic nervous system pharmacology allows students to integrate the physiology and neuroscience they have learned elsewhere with the pharmacology they are learning and prepares them to understand the autonomic effects of other drugs. This is especially important for the cardiovascular and central nervous system drug groups. However, chapters can be used equally well in courses and curricula that present these topics in a different sequence.

Within each chapter, emphasis is placed on discussion of drug groups and prototypes rather than offering repetitive detail about individual drugs. Selection of the subject matter and the order of its presentation are based on the accumulated experience of teaching this material to thousands of medical, pharmacy, dental, podiatry, nursing, and other health science students.

Major features that make this book particularly useful in integrated curricula include sections that specifically address the clinical choice and use of drugs in patients and the monitoring of their effects—in other words, *clinical pharmacology* is an integral part of this text. Lists of the commercial preparations available, including

trade and generic names and dosage formulations, are provided at the end of each chapter for easy reference by the house officer or practitioner writing a chart order or prescription.

## Significant revisions in this edition include:

- In addition to the Case Studies used to open many chapters, Case Study Answers at the end of these chapters provide an introduction to the clinical applications of the drugs discussed.
- A Drug Summary Table is placed at the conclusion of most chapters; these provide a concise recapitulation of the most important drugs.
- Many new illustrations in full color provide significantly more information about drug mechanisms and effects and help to clarify important concepts.
- Major revisions of the chapters on sympathomimetic, sympathoplegic, antipsychotic, antidepressant, antidiabetic, anti-inflammatory, and antiviral drugs, prostaglandins, nitric oxide, hypothalamic and pituitary hormones, and immunopharmacology.
- Continued expansion of the coverage of general concepts relating to newly discovered receptors, receptor mechanisms, and drug transporters.
- Descriptions of important new drugs released through August 2011.

An important related educational resource is *Katzung & Trevor's Pharmacology: Examination & Board Review*, ninth edition (Trevor AJ, Katzung BG, & Masters SB: McGraw-Hill, 2010). This book provides a succinct review of pharmacology with over one thousand sample examination questions and answers. It is especially helpful to students preparing for board-type examinations. A more highly condensed source of information suitable for review purposes is *USMLE Road Map: Pharmacology*, second edition (Katzung BG, Trevor AJ: McGraw-Hill, 2006).

This edition marks the 30th year of publication of *Basic & Clinical Pharmacology*. The widespread adoption of the first eleven editions indicates that this book fills an important need. We believe that the twelfth edition will satisfy this need even more successfully. Spanish, Portuguese, Italian, French, Indonesian, Japanese, Korean, and Turkish translations are available. Translations into other languages are under way; the publisher may be contacted for further information.

I wish to acknowledge the prior and continuing efforts of my contributing authors and the major contributions of the staff at Lange Medical Publications, Appleton & Lange, and McGraw-Hill,

and of our editors for this edition, Donna Frassetto and Rachel D'Annucci Henriquez. I also wish to thank my wife, Alice Camp, for her expert proofreading contributions since the first edition.

This edition is dedicated to the memory of James Ransom, PhD, the long-time Senior Editor at Lange Medical Publications, who provided major inspiration and invaluable guidance through the first eight editions of the book. Without him, this book would not exist.

Suggestions and comments about *Basic & Clinical Pharmacology* are always welcome. They may be sent to me in care of the publisher.

Bertram G. Katzung, MD, PhD  
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December, 2011

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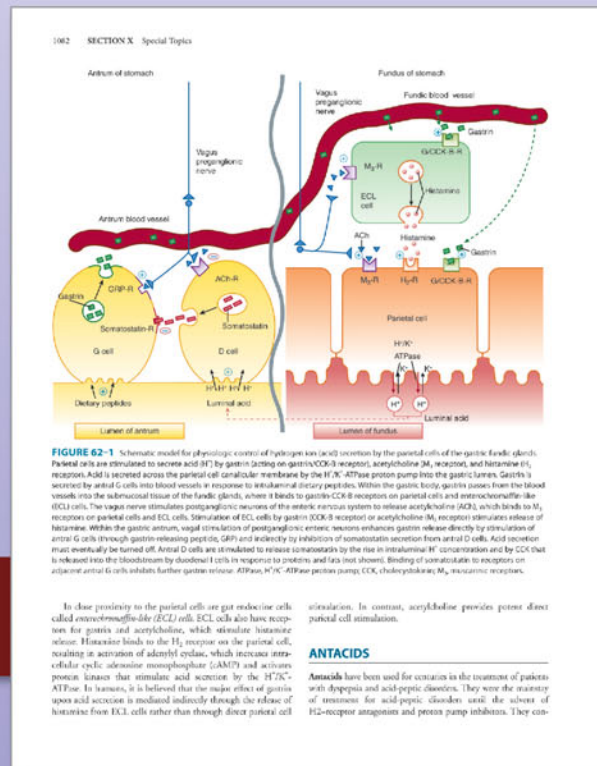
# Key Features of *Basic & Clinical Pharmacology, 12e*

*The most comprehensive, authoritative, and engaging pharmacology textbook for students in the health sciences*

## Key Features

- More than 300 full-color illustrations
- Emphasis is placed on discussion of drug groups and prototypes within each chapter
- NEW case studies open several chapters, adding clinical relevance to the material
- NEW case study answers at the end of the chapters provide an introduction to the clinical application of the drugs discussed
- NEW drug summary tables conclude most chapters, providing a concise summary of the most important drugs
- Expanded coverage of general concepts relating to newly discovered receptors, receptor mechanisms, and drug transporters
- Lists of the commercial preparations available, including trade and generic names and dosage formulations, are provided at the end of each chapter
- Selection of the material and order of presentation is based on the author's years of experience in teaching this material to thousands of students
- Material is organized according to the sequence used in most pharmacology courses

**Hundreds of full-color illustrations enrich the text**



306 SECTION V Drugs That Act on the Central Nervous System

SUMMARY Sedative-Hypnotics				
Subclass and Examples	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
<b>BENZODIAZEPINES</b> • Alprazolam • Clonazepam • Clobazam • Clonazepam • Lorazepam • Oxazolone • Temazepam • Triazolam	Bind to specific GABA <sub>A</sub> receptors, increase duration of GABA-mediated inhibition of neuronal firing, and increase frequency of GABA-mediated chloride ion channel opening—cause transient neuroinhibition	Decreased/depressed effects on the CNS including anxiety, arousal, aggression, and motor activity; anxiolysis, sedation, muscle relaxation, respiratory depression	Anxiety, seizures, spastic muscle contractions, alcohol withdrawal, preoperative sedation, induction of labor, muscle relaxation, postoperative sedation	Full from 1-4 hr and activity rapidly reversible—some active metabolites; specific receptors of CNS depression effects—dependence, tolerance, withdrawal; CYP2C19 converts with additional nonactive drug
<b>BENZODIAZEPINE ANTAGONIST</b> • Flumazenil	Antagonist of benzodiazepine binding sites on the GABA <sub>A</sub> receptor	Blocks actions of benzodiazepines and antagonizes but not other sedative/hypnotic drugs	Management of benzodiazepine overdose	10-15 min full 0.5-1 h activity
<b>BARBITURATES</b> • Amobarbital • Propofol • Thiopental • Thiopental • Thiopental	Bind to specific GABA <sub>A</sub> receptors, increase duration of GABA-mediated inhibition of neuronal firing, and increase frequency of GABA-mediated chloride ion channel opening—cause transient neuroinhibition	Decreased/depressed effects on the CNS including anxiety, arousal, aggression, and motor activity; anxiolysis, sedation, muscle relaxation, respiratory depression	Anesthesia (propofol), sedation, preoperative sedation, induction of labor, muscle relaxation, postoperative sedation	Full from 1-4 hr and activity rapidly reversible—some active metabolites; specific receptors of CNS depression effects—dependence, tolerance, withdrawal; CYP2C19 converts with additional nonactive drug
<b>NEURIPYPTICS</b> • Gabapentin • Pregabalin	Inhibit synthesis in a subpopulation of GABA <sub>A</sub> receptors, which are heteropentamers composed of two $\alpha$ 1 and three $\beta$ 2 subunits	Reduce synthesis of GABA, which has anxiolytic effects, and also after pain transmission, hyperalgesia	Seizure disorders, neuropathic pain, postoperative sedation, difficulty in falling asleep	CNS activity—short half-life—CYP2C19 converts to active metabolite; specific receptors of CNS depression effects—dependence, tolerance, withdrawal; CYP2C19 converts with additional nonactive drug
<b>MELANOCORTIN RECEPTOR AGONIST</b> • Orexin-1	Agonist of MC4R and MC5R receptors in hypothalamus, which are heteropentamers composed of two $\alpha$ 1 and three $\beta$ 2 subunits	Reduces food intake, increases energy expenditure, and increases metabolic rate	Obesity, diabetes, metabolic syndrome, difficulty in falling asleep	CNS activity—short half-life—CYP2C19 converts to active metabolite; specific receptors of CNS depression effects—dependence, tolerance, withdrawal; CYP2C19 converts with additional nonactive drug
<b>5-HT<sub>2A</sub> RECEPTOR ANTAGONIST</b> • Ketanserin	Antagonist of 5-HT <sub>2A</sub> receptors in hypothalamus, which are heteropentamers composed of two $\alpha$ 1 and three $\beta$ 2 subunits	Reduces food intake, increases energy expenditure, and increases metabolic rate	Obesity, diabetes, metabolic syndrome, difficulty in falling asleep	CNS activity—short half-life—CYP2C19 converts to active metabolite; specific receptors of CNS depression effects—dependence, tolerance, withdrawal; CYP2C19 converts with additional nonactive drug

Drug Summary Tables conclude most chapters

CHAPTER 49

## Antiviral Agents

Sharon Safrin, MD

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**CASE STUDY**

A 35-year-old white woman who recently tested seronegative for both HIV and hepatitis B virus antigen is referred for evaluation. She is feeling well overall but reports a 25-pick-year smoking history. She drinks 3-4 beers per week and has no known medications. Allergies: She has a history of hives and is currently receiving methotrexate. Physical examination reveals normal vital signs and no

abnormalities. White blood cell count is 10,000 cells/mm<sup>3</sup> with a normal differential; hemoglobin is 11.4 g/dL; all liver function tests are within normal limits; CD4 cell count is 270 cells/mm<sup>3</sup>; and viral load (HIV RNA) is 10,000 copies/mL. What other laboratory tests should be ordered? Which antiretroviral medications would you begin?

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Virus are obligate intracellular parasites that replicate dependently on synthesis processes of the host cell. Therefore, to be effective, antiviral agents must either block viral entry into or exit from the cell or be active inside the host cell. As a secondary, non-specific inhibition of viral replication may interfere with host cell function and result in toxicity.

Progress in antiviral chemotherapy began in the early 1970s, when the search for anticancer drugs produced several new compounds capable of inhibiting viral RNA synthesis. The first generation antiviral agents, nucleoside analogs and nucleoside triphosphate diphosphate diphosphate, also inhibited host cell DNA as well as viral DNA that resulted in too toxic to systemic use. However, with specific antiviral agents used specifically for the treatment of herpes viruses.

Knowledge of the mechanisms of viral replication has provided insights into critical steps in the viral life cycle that can serve as potential targets for antiviral therapy. Recent research has focused on identifying agents with greater selectivity, higher potency, in vivo stability, and reduced toxicity. Antiviral therapy is now available for herpesviruses, hepatitis C virus (HCV), hepatitis B virus (HBV), papillomavirus, influenza, and human immunodeficiency virus (HIV). Antiviral drugs share the common property of being toxic to the virus but not to the host cell, and they do not affect host cells. Effective antiviral therapy requires knowledge of the host cell's ability to replicate and the ability to inhibit viral replication. Antiviral therapy for herpesviruses, hepatitis C virus (HCV), hepatitis B virus (HBV), papillomavirus, influenza, and human immunodeficiency virus (HIV). Antiviral drugs share the common property of being toxic to the virus but not to the host cell, and they do not affect host cells. Effective antiviral therapy requires knowledge of the host cell's ability to replicate and the ability to inhibit viral replication.

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**ACRONYMS & OTHER NAMES**

- AZT Zalcitabine
- 3TC Lamivudine
- AZT Zalcitabine (proprionyl isobutyrate prodrug)
- CMV Cytomegalovirus
- CYP Cytochrome P450
- dAT Didanosine
- dCT Zalcitabine
- dIT Zalcitabine
- EBV Epstein-Barr virus
- FTC Emtricitabine
- HBsAg Hepatitis B antigen
- HBV Hepatitis B virus
- HCV Hepatitis C virus
- HPV-6 Human papillomavirus-6
- HPV Human immunodeficiency virus
- HSV Herpes simplex virus
- NIHNI Nucleoside reverse transcriptase inhibitor
- NTI Nucleoside/nucleotide reverse transcriptase inhibitor
- PI Protease inhibitor
- RT Regulator of transcription
- SVR Sustained viral response
- USTIA1 UDP-glucuronosyl transferase 1A1
- VZV Varicella-zoster virus

Case studies are included in selected chapters

CHAPTER 22 Sedative/Hypnotic Drugs 307

### PREPARATIONS AVAILABLE

<b>BENZODIAZEPINES</b> <b>Alprazolam (generic, Xanax)</b> Oral 0.25, 0.5, 1 mg tablets; extended-release tablets; and orally disintegrating tablets; 1.5 mg oral solution <b>Chlordiazepoxide (generic, Librium)</b> Oral 5, 10 mg capsules <b>Clonazepam (generic, Rivotril)</b> Oral 0.5, 1 mg tablets and oral solution Oral extended-release 15, 30 mg tablets <b>Clobazam (generic, Onfi)</b> Oral 5, 10 mg tablets; 100 mg oral solution <b>Clonazepam (generic, Klonopin)</b> Oral 0.5, 1 mg tablets; 100 mg oral solution; 1 mg orally disintegrating tablets <b>Etiopiam (generic, Valium)</b> Oral 5, 10 mg tablets; 1 mg oral solution Parenteral 1 mg/mL for injection <b>Ethchlorvynol (generic, Proletan)</b> Oral 1 mg tablets <b>Flurazepam (generic, Dalmane)</b> Oral 15, 30 mg tablets <b>Lorazepam (generic, Ativan)</b> Oral 0.5, 1 mg tablets; 1 mg oral solution Parenteral 1 mg/mL for injection <b>Midazolam (generic, Versed)</b> Oral 7.5 mg syrup Parenteral 1 mg/mL for 1.5, 3, 6 mg/mL for injection <b>Oxazolone (generic)</b> Oral 15, 30 mg capsules <b>Oxazolone (brand)</b> Oral 15, 30 mg tablets <b>Temazepam (generic, Restoril)</b> Oral 0.25, 0.5, 1 mg tablets <b>Triazolam (generic, Halcion)</b> Oral 0.125, 0.25 mg tablets	<b>BARBITURATES</b> <b>Amobarbital (generic, Amytal)</b> Parenteral 100 mg in 10 mL; 100 mg tablets for injection <b>Mephobarbital (brand, Mebaral)</b> Oral 15, 30 mg tablets <b>Phenobarbital (generic, Nembutal, Luminal)</b> Oral 10, 20, 30 mg tablets; 4 mg/mL oral solution; 10, 100, 300 mg oral suspension Parenteral 10 mg/mL for injection <b>Phenylethylmalonate (generic, Luminal Sodium)</b> Oral 15, 30, 60, 90 mg tablets; 60 mg capsules; 15, 30 mg/mL oral solution Parenteral 100 mg/mL for injection <b>Secoobarbital (generic, Seconal)</b> Oral 100 mg tablets
<b>BENZODIAZEPINE ANTAGONIST</b> <b>Flumazenil (generic, Anexate)</b> Parenteral 1 mg/mL for IV injection	<b>MISCELLANEOUS DRUGS</b> <b>Propofol (generic, Diprivan)</b> Oral 1, 2 mg tablets Parenteral 1 mg/mL for 1.5, 3, 6 mg/mL for injection; 10 mg/mL for 10, 20, 30 mg capsules; 10 mg/mL for 10, 20, 30 mg tablets; 10 mg/mL for 10, 20, 30 mg capsules; 10 mg/mL for 10, 20, 30 mg tablets <b>Propofol (brand, Diprivan)</b> Oral 1, 2 mg tablets Parenteral 1 mg/mL for 1.5, 3, 6 mg/mL for injection; 10 mg/mL for 10, 20, 30 mg capsules; 10 mg/mL for 10, 20, 30 mg tablets; 10 mg/mL for 10, 20, 30 mg capsules; 10 mg/mL for 10, 20, 30 mg tablets <b>Propofol (brand, Diprivan)</b> Oral 1, 2 mg tablets Parenteral 1 mg/mL for 1.5, 3, 6 mg/mL for injection; 10 mg/mL for 10, 20, 30 mg capsules; 10 mg/mL for 10, 20, 30 mg tablets; 10 mg/mL for 10, 20, 30 mg capsules; 10 mg/mL for 10, 20, 30 mg tablets <b>Propofol (brand, Diprivan)</b> Oral 1, 2 mg tablets Parenteral 1 mg/mL for 1.5, 3, 6 mg/mL for injection; 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