Chapter 15

Research

Audit and research

Research on humans should be subject to ethical committee review. Sometimes there is a blurred distinction between audit or quality assurance activities and research. Pharmacists need to consider projects carefully and ensure that they comply with local requirements. The following may help to distinguish research from audit and quality assurance.

Audit (which might not need to go to ethics committee review)

- Measures the process and outcome of care.
- Is not randomized.
- Is usually initiated and conducted by those providing the clinical service.
- Involves review of recorded data by those entitled to have access to such data.
- May include patient questionnaires.

Research (which should go to ethics committee review if it involves patients or volunteers)

- Randomized studies.
- Data collection if outside personnel can access sensitive information about patients.
- Interventions involving contact with patients by a health professional previously unknown to them.
- Questionnaires asking for personal data or sensitive sociodemographic details.
- If there is an intention to publish data as research.
- If pharmaceutical data are collected (other than post-marketing surveillance).
- If patients or volunteers have any procedure or treatment additional to normal medical care.
- If patient samples of any sort are taken additional to normal medical care.

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Writing a research proposal

Structure of a research proposal

- Title of project
- Purpose of project
- Background of project
- Central research question(s)
- Research design
- Data analysis
- Timetable
- Research staff required
- Resources required
- Proposed budget
- References

Title of project

- Descriptive
- Clear
- Succinct
- Use recognizable keywords
- Comprehensible (to non-specialists)
- Should not imply an expected outcome

Examples

- 'A randomized controlled trial of amitriptyline in chronic pain'
- 'A controlled evaluation of advice giving for low back pain'
- 'A descriptive study of the needs of patients on an orthopaedic surgery ward'

Purpose of the project

- Why undertake the project?
- Who will benefit?
- Academic potential/contribution?
- Clinical potential/contribution?
- Patient potential/contribution?
- What gaps are likely to be filled?

Background of project

- Literature review
- Critical appraisal of literature/evidence
- Establish scientific adequacy of evidence
- Establish clinical and social adequacy of evidence
- Identify positive evidence and the potential to support, replicate, or challenge it
- Identify negative evidence and the potential to support, replicate, or challenge it
- Identify uncertain evidence and the potential to clarify, support, or reject it
- Identify lack of evidence and potential to remedy this
- Justify research questions

Research questions

- Clear
- Specific
- Distinctive
- Comprehensible (to self and others)
- Answerable
- Feasible (scientifically and financially)

Research design

- Type of design:
  - randomized controlled trial
  - matched comparison
  - cohort study
  - single case study
  - descriptive/ethnographic
- Sampling frame
- Sample selection criteria
- Baseline and follow-up strategy
- Measures/data to be collected (methods/outcome/satisfaction/costs)
- Access to data arrangements (Data Protection Act might apply)
- Ethical considerations—research often requires approval from an ethics committee or equivalent body (see 📖 p.304)

Data analysis

- How data will be stored:
  - manually and computerized
  - coded
  - entered
  - confidentiality and anonymity
- How data will be retrieved from computer?
- How data will be manipulated:
  - descriptive versus inductive
  - univariate/bivariate/multivariate analysis
  - tests of significance
  - qualitative data handling
- Which statistical/epidemiological package (e.g. SPSS/EpiInfo/NUDIST)?
- Data presentation strategy
  - report writing strategy (eg report/journal publications/book/meeting presentation/poster)

Timetable

- Preparation time
- Start/baseline data collection
- Follow-up data collection
- End of data collection
- Data retrieval time
- Data manipulation and analysis
- Report preparation, writing, and dissemination
- Do not underestimate the time involved—be realistic and keep to the schedule

Research staff required

- Self
- Research assistants
- Interviewers
- Secretarial/administrative support
- Data entry, retrieval, and handling staff
- Consultancies (statistician/specialist advice/support)

Resources required

- Staff
- Accommodation (office space and storage space)
- Equipment:
  - computer hardware/software
  - telephones/fax/email
  - furniture/filing cabinets/storage
  - audio/video recording machinery
  - specialist/technical equipment
- Laboratory time/access
- Books, journals, and library services
- Printing and stationery
- Postage
- Travel—both staff and reimbursement for participants in the study
- Overheads (staff and agency)

References

Provide supporting references in a standard format, such as Vancouver (see 🕮 p.309).

Citations in documents and articles for publication

A variety of styles are used to cite publications in the medical literature. Editors of several medical journals have established guidelines for the format of manuscripts submitted to their journals. This group, known as the International Committee of Medical Journal Editors (ICMJE), has broadened its focus beyond manuscript and reference formatting to include ethical principles related to publication in biomedical journals. Many journals now follow ICMJE's *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication* (www.icmje.org/). Review of the *Uniform Requirements* is beyond the scope of this book but it should be consulted by those preparing materials for publication.

The commonly used methods of citation are listed here with examples. For further details see the BMA website.[1]

Harvard style

In the Harvard style references are cited using the author–date system. For example:

- Journal/book articles—in the text:
  - Davies and Mehan (1988) have argued …
- Journal/book articles—in the reference list:
  - Davies, P.T. and Mehan, H. (1988). Professional and family understanding of impaired communication. *British Journal of Disorders of Communication* **23**, 141–51.
- Books—in the text:
  - Davies (1983) has argued that …
- Books—in the reference list:
  - Davies, PT (1983). *Alcohol Problems and Alcohol Control in Europe*. London: Croom Helm.

List all authors (up to a maximum of six) in the reference list.

Vancouver style

In the Vancouver style references are cited using the author–number system:

- Journal/book articles—in the text:
  - Onghena and Van Houdenhove[4] have argued …
- Journal/book articles—in the reference list:
  - 4. Onghena P, Van Houdenhove B. Antidepressant induced analgesia in chronic pain: a meta-analysis of 39 placebo controlled studies. *Pain* 1992 May; **49**(2): 205–19.
- Books—in the text:
  - Colson and Armour[5] have argued …
- Books—in reference list:
  - 5. Colson JH, Armour WJ. *Sports Injuries and their Treatment* (2nd rev. edn). London: S Paul; 1986.
  - List all authors (up to a maximum of six) in the reference list.

1 http://www.bma.org.uk/library_services/ask_for_help/libraryreferencestyles.jsp

Personal bibliographic databases

Personal bibliographic databases are simply structured database files with some useful features that enable references to be quickly stored, retrieved, or inserted into word-processed documents. The basic layout of the database is designed to handle information published in various formats (e.g. journal articles or books) and the fields are set up to hold that information. There are additional fields that include sections for keywords and reference numbers. The simplest use of the database is to manually add information into the fields in a logical sequence. The data are held as records that can then be searched using a variety of options, such as author, date of publication, or keywords. It is then a simple task to assign a number to the record that matches a number added to a stored original article (e.g. in numerical order of the collection) and subsequently to retrieve the hard copy of a reference by searching for keywords, for example. Databases of many thousands of papers can be built up in this way and single articles identified in seconds. For example, a single reference in a ProCite® database of 20 000 records can be found in <5 seconds.

There are some useful additions that make this type of software particularly valuable. First, searches that have been carried out electronically using a database, such as MEDLINE, can be downloaded directly into the personal bibliographic database using a linking software package, such as Bibliolinks. Translators are available for most of the commonly used databases, and this facility enables a database of useful information to be created quickly without re-keying the information. The full record is usually imported, including the abstract, thus extending the search possibilities within the personal database.

Secondly, all the software packages have the means for either simple or complex searches. In ProCite® the following options are available.

To search a database, it is possible to build a 'search expression' in the text box. You can type the text or use the 'Fields', 'Operators', and 'Terms' buttons to help build your search expression. For example, you could enter: AUTHOR = Smith and KEYWORDS = Asthma.

It is possible to search by date, or a range of dates. You can save your search expression with the 'Expressions' button, so you can perform the same search again after more records are entered, or you can save the list of records that results from your current search by highlighting them and using the 'Group' menu to save them to a 'Group'.

The third key feature is the ability to link a manuscript to the database to generate a reference list. This task, which is usually time-consuming and tedious, is quickly performed because the word-processing package interacts to find the references mentioned, marks the text in the appropriate way (e.g. superscript number), and produces the reference list. Various styles of reference are available, so if your manuscript in Vancouver style, for example, is rejected by your favourite journal, it can be submitted to another journal that might require Harvard formatting with ease.

Author Analytic (01): Carroll, D.// Jadad, A.// King, V.// Wiffen, P.// Glynn, C.// McQuay, H.

Article Title (04): Single-dose, randomized, double-blind, double-dummy cross-over comparison of extradural and i.v. clonidine in chronic pain

Journal Title (03): Br J Anaesth
Date of Publication (20): 1993
Volume Identification (22): 71
Issue Identification (24): 5
Page(s): 665–9
ISSN (40): 0007–0912
Notes (42): HC

Abstract (43): We studied 10 patients with chronic back pain who had claimed benefit with a previous extradural dose of clonidine 150 micrograms combined with local anaesthetic. We compared a single dose of clonidine 150 micrograms given by either the extradural or i.v. route in a double-blind, randomized, double-dummy and cross-over fashion, with 80% power to detect a difference in the analgesic effect of the two routes. Pain intensity, pain relief, adverse effects, mood, sedation and vital signs were assessed by a nurse observer. I.v. clonidine produced significantly ($P < 0.04$) greater analgesia than extradural clonidine in one of the five analgesic outcome measures. Clonidine given by either route produced statistically significant sedation and significant decreases in arterial pressure and heart rate. In this study, extradural clonidine had no significant clinical advantages compared with i.v. clonidine; clonidine 150 micrograms by either route produced a high incidence of adverse effects.

Keywords (45): Yes/Chronic non-malignant pain/Pharmacolgical intervention/Adult/Aged/Analgesia, Epidural/Clonidine administration and dosage/Clonidine adverse effects/Double Blind Method/Injections, Intravenous/Middle Age/Pain Measurement/Back Pain drug therapy/Clonidine therapeutic use/Comparative Study/Female/Human/Male/Support, Non U.S. Gov't

Fig. 15.1 Example from ProCite®.

The reference shown in Fig. 15.1 appears as follows when presented in Vancouver format:

Carroll D, Jadad A, King V, Wiffen P, Glynn C, McQuay H (1993). Single-dose, randomized, double-blind, double-dummy cross-over comparison of extradural and i.v. clonidine in chronic pain. *Br J Anaesth* **71**(5): 665–9.

It is beyond the scope of this book to recommend a particular package, but a number of are available, including Reference Manager®, ProCite®,

Idealist®, and EndNote®. Other less well-known packages include Papyrus®, Citation 8®, and RefWorks®. Some are web-based applications, i.e. the reference database is accessible from any computer that has access to the internet. Other programs store the reference databases on the user's computer or a portable storage device and are accessible whether internet access is available or not.

Most reference manager software products offer a trial period. It is recommended that prospective buyers define their own needs and find the product that is best suited for them.

Chapter 16

Therapy-related issues: gastrointestinal system

Diarrhoea

Description and causes

- 'Diarrhoea' is a term generally understood to mean an ↑ frequency of bowel movement relative to normal for an individual patient.
- The normal bowel habit in Western society lies somewhere in the range between two bowel actions/week and three bowel actions/day.
- The mechanisms that result in diarrhoea are varied and include ↑ secretion or ↓ absorption of fluid and electrolytes by cells of the intestinal mucosa and exudation resulting from inflammation of the intestinal mucosa.
- Diarrhoea is a non-specific symptom that is a manifestation of a wide range of GI disorders, including inflammatory bowel disease, irritable bowel syndrome, GI malignancy, a variety of malabsorption syndromes, and acute or subacute intestinal infections and infestations.
- Diarrhoea can be an unwanted effect of almost any drug, particularly those listed in the next section.

Medications commonly causing diarrhoea

Osmotic (drugs that create a hypertonic state in the intestine)

- Acarbose, magnesium salts, and antibiotics.

Secretory (↑ intestinal ion secretion or inhibit normal active ion absorption)

- Antineoplastics, digoxin, metformin, NSAIDs, misoprostol, and olsalazine.

Disturbed motility (leading to shortened transit time)

- Erythromycin, levothyroxine

Exudative (drugs that cause inflammation and ulceration)

- Antineoplastics, NSAIDs, and simvastatin

Malabsorption or impaired digestion of fat or carbohydrates

- Aminoglycosides, colestyramine, metformin, orlistat, and tetracyclines

Microscopic colitis (drugs causing a submucosal band of collagen in the intestine, resulting in a watery diarrhoea)

- Cytotoxic agents, budesonide, carbamazepine, ciclosporin, co-beneldopa, ranitidine, and simvastatin.

All patients presenting with diarrhoea should be questioned about the relationship between symptoms and changes in medications.

If an underlying cause of diarrhoea can be identified, management is directed at the cause rather than the symptom of diarrhoea.

Treatment

Chronic diarrhoea

The treatment of chronic diarrhoea depends on controlling the underlying disease.

Acute diarrhoea

Fluid and electrolyte therapy

Even in the presence of severe diarrhoea, water and salt continue to be absorbed by active glucose-enhanced sodium absorption in the small intestine. Oral replacement solutions are effective if they contain balanced quantities of sodium, potassium, glucose, and water. Glucose is necessary to promote electrolyte absorption.

Proprietary soft drinks and fruit juices may be inadequate treatment for individuals in whom dehydration poses a significant risk—e.g. the elderly and patients with renal disease.

In adults, an oral rehydration solution should be considered for patients with mild to moderate dehydration (loss of <6% of body weight). Solutions should be made up freshly according to manufacturers' recommendations, refrigerated, and replaced every 24h.

Several proprietary rehydration products are available and are made up according to brand recommendations. The recommended range of concentrations for rehydration solutions for use are as follows:

- sodium 50–60mmol/L
- potassium 20–35mmol/L
- glucose 80–120mmol/L.

For adults, encourage 2–3L of rehydration solution orally to be taken over 24h. This will provide 100–180mmol of sodium and 40–105mmol of potassium. Once rehydration is complete, further dehydration is prevented by encouraging the patient to drink normal volumes of an appropriate fluid and by replacing continuing losses with an oral rehydration product.

Drug therapy

Antimotility drugs may be of symptomatic benefit in adults with mild or moderate acute diarrhoea. Their most valuable role is in short-term control of symptoms during periods of maximum social inconvenience (e.g. travel and work). They are contraindicated in patients with severe diarrhoea, and in patients with severe inflammatory bowel disease or dilated or obstructed bowel. However, antimotility drugs are also sometimes useful for control of symptoms if treatment of the underlying cause is ineffective or the cause is unknown. Antimotility drugs are never indicated for management of acute diarrhoea in infants and children <12.

If an antimotility drug is considered appropriate, it is reasonable to use one of the following regimens.

- Loperamide 4mg orally initially, followed by 2mg orally after each unformed stool (maximum of 16mg/daily).
- Diphenoxylate 5mg + atropine 0.05mg orally three to four times daily initially (↓ dose as soon as symptoms improve).
- Codeine phosphate 30–60mg orally up to four times daily.

Adsorbents, such as kaolin and activated charcoal have not been shown to be of value in the treatment of acute diarrhoea. They could interfere with absorption of other drugs and should not be used.

Antibacterials are rarely indicated in uncomplicated infective diarrhoea, except to treat properly diagnosed enteric infections such as dysentery and antibacterial-associated colitis.

Diarrhoea can reduce the absorption of medicines. Drugs that may be affected clinically significantly include antiepileptics, modified release formulations, antidiabetic agents, anticoagulants, antimalarials, anti-retrovirals, and oral contraceptives.

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Constipation in adults

Description and causes of constipation in adults

- Defined as a ↓ frequency of defecation.
- The normal frequency of bowel motions in western countries varies from three times/day to twice/wk.
- A person might complain of constipation for the following reasons.
  - Defecation occurs less frequently than usual.
  - Stools are harder than usual.
  - Defecation causes straining.
  - Sense of incomplete evacuation.

There are a large number of causes of constipation, ranging from common dietary problems to mechanical obstruction, including the adverse effects of many commonly used drugs. One of the most common causes is a low-residue diet.

Some medications commonly causing constipation

- Aluminium- and calcium-containing antacids
- Amiodarone
- Anticholinergic agents (e.g. tricyclic antidepressants, antipsychotics and antispasmodics, antiparkinsonian agents)
- Clozapine, olanzapine, risperidone and quetiapine
- Iron preparations
- Diuretics
- Lithium
- NSAIDs
- Opioids
- Calcium-channel blockers

Changing or stopping these drugs might be all that is required to restore normal bowel function.

Most of the factors predisposing to constipation are potentially magnified or compounded in the older patient. In this group, particularly, prolonged constipation can lead to faecal impaction, causing urinary and faecal overflow incontinence. The latter is sometimes misdiagnosed and treated as diarrhoea. It is an avoidable cause of hospital admission.

Treatment of constipation in adults

Patients, especially if ambulant and otherwise healthy, should be encouraged to control their bowel activity by attention to diet and exercise. The diet should contain adequate amounts of fibre and fluid. Physical exercise has been shown to ↓ intestinal transit time and is believed to stimulate regular bowel movements.

If these measures are ineffective, intermittent or regular use of a laxative might be necessary (Table 16.1). The duration of treatment with laxatives should be limited to the shortest time possible. The undesirability of long-term laxative use should be explained to the patient.

Diet

The major lifestyle factor leading to constipation is inadequate dietary fibre intake. Dietary fibre consists of plant complex carbohydrates that

escape digestion in the small intestine and are only partly broken down by bacterial enzymes in the large intestine. The ingestion of dietary fibre ↑ stool bulk by ↑ both solid residue and stool water content. This results in ↓ intestinal transit time and ↓ water absorption in the large bowel, resulting in stools that are softer, wetter, and easier to pass.

The recommended amount of dietary fibre is 30g/day. The fibre content of the diet should be built up gradually to avoid adverse effects, such as bloating or flatulence. Patients should be encouraged to choose a wide variety of fibre sources (e.g. wholegrain or wholemeal products such as breads, cereals, pastas and rice, fruits and vegetables, legumes, seeds and nuts) rather than adding a few very high fibre foods (e.g. unprocessed bran) to the diet. Ensure that adequate fluid intake is encouraged.

Drug therapy

There is little clinical evidence on which to judge the relative effectiveness and tolerability of individual laxatives. Therefore choice should be based on symptoms, patient preferences, side effects, and cost of medicines.

First-line therapy

If dietary management is not sufficient, bulk-forming agents are the laxatives of choice for mildly constipated individuals. Provided that good fluid intake is maintained, use the following agents:

- oral bulk-forming agents

The effect of bulk-forming laxatives is usually apparent within 24h, but 2–3 days of medication might be required to achieve the full effect.

Second-line therapy

- Osmotic laxative—lactulose syrup 10–30mL orally twice or three times daily. Lactulose syrup contains free lactose and galactose and therefore it should be used with caution in patients with diabetes mellitus and is contraindicated in galactosaemia. The laxative can take 48h to work, so it must be taken regularly.
- Stimulant laxative—senna 7.5mg or bisacodyl 5mg, one or two tablets daily (interchangebly). The agents used for second-line therapy can also be used as first-line therapy in acute illness or for hospitalized patients.
- Although stool-softening agents, such as docusate salts, are often used in the treatment of constipation, they have limited effectiveness as monotherapy.

Third-line therapy

If constipation is resistant to the first- and second-line therapies, there should be a re-evaluation of the underlying cause(s), including impaction. For further therapy, use one of the following regimens:

- Magnesium sulphate 5–15g (5–15mL) orally in water daily.
- A stimulant agent (e.g. senna 30mg or bisacodyl 20mg) orally daily at night.

If required, consider the following regimens.

- Glycerin suppository rectally (allow to remain for 15–30min).
- Phosphate enema rectally.

Magnesium salts should not be used in pregnant women or patients with impaired renal function.

Fourth-line therapy

In a minority of patients all three therapies are unsuccessful and repeated enemas, macrogols (polyethylene glycol, e.g. Laxido® or Movicol®, sodium phosphate or sodium picosulphate bowel preparations) and/or manual evacuation might be required, sometimes after admission to hospital. Laxido®/Movicol®, 1–3 sachets daily in divided doses usually for ≤2wks; each sachet should be dissolved in 125mL of water.

Opioid-induced constipation

When an opioid is first prescribed, either lactulose and senna or co-danthrusate (one or two capsules) at night should be added as a prophylactic measure. (Sometimes the dosage must be ↑ to two capsules twice daily acutely, and then reduced to one or two at night).

If the patient is already constipated, ↑ the dosage to co-danthrusate two capsules at night; adjust the dose according to response, up to a maximum of three capsules three times daily.

If the maximum dose is ineffective, ↓ the dose by 50% and add an osmotic laxative—e.g. lactulose 20–30mL twice daily or Movicol® one sachet twice daily.

Table 16.1 Laxative choice

Constituent(s), form, and preparation	Dose (adult dose, unless otherwise specified)	Time to onset
Bulk-forming laxatives		
Note: it is recommended that bulk-forming agents be taken with adequate fluid		
Ispaghula granules	1 sachet or 5mL spoonful, twice daily Child 6–12yrs: 50% adult dose	Usually 24h, 2–3 days for full effect
Sterculia	1–2 heaped 5mL spoonfuls twice daily Child 6–12yrs: 50% adult dose	Usually 24h, 2–3 days for full effect
Osmotic laxatives		
Lactulose syrup	15–30mL daily, in one or two doses initially Child, <1yr: 5mL Child, 1–6yrs: 10mL Child, 7–14yrs: 15mL daily initially	1–2 days
Magnesium sulphate mixture	5–15mL in 250mL water	1h

Table 16.1 (*Contd.*)

Constituent(s), form, and preparation	Dose (adult dose, unless otherwise specified)	Time to onset
Macrogols	1–3 sachets in 125mL water daily	1h
Phosphate enemas	See product information	2–5min
Stool-softening laxatives		
Docusate tablets	200mg twice daily	1–3 days
Arachis oil (rectal) (contraindicated in peanut allergy)	See product information	1 day
Stimulant laxatives		
Bisacodyl 5mg tablets	1–2 tablets daily	6–12h
Bisacodyl 10mg suppositories	1 suppository daily	15–60min
Senna 7.5mg tablets	2–4 tablets daily Child >6 years: 50% adult dose	6–12h
Co-danthrusate (opioid-induced constipation)	1–3 capsules at night	6–12h
Lubricant laxatives		
Glycerol/glycerin suppositories	1 suppository, as required	15–30min
Liquid paraffin oral emulsion	10–30mL at night	8–12h
Note: prolonged use of liquid paraffin oral emulsion can cause deficiency of fat-soluble vitamins and is associated with lipoid pneumonia		
Bulk-forming combined with stimulant laxatives		
Note: it is recommended that bulk-forming agents be taken with adequate fluid		
Frangula+sterculia granules	1–2 heaped teaspoonsful once or twice daily	6–12h

Management of nausea and vomiting

Nausea and vomiting are common and distressing symptoms, which can lead to the following clinical conditions:

- poor hydration and nutrition
- weight loss
- depression
- ↑ length of stay
- poor adherence to oral medicines.

Causes of nausea and vomiting

- Chemical:
  - exogenous—e.g. microbial toxins and drugs
  - endogenous—e.g. uraemia and hypercalcaemia.
- CNS:
  - emotional and anxiety
  - CNS lesions
  - vestibular
  - ↑ intracranial pressure.
- Obstructive:
  - constipation
  - GI tumours

Factors that can ↑ the risk or severity of nausea and vomiting include the following:

- ♀
- tendency to nausea and vomiting (e.g. motion sickness and drug intolerance)
- non-smoker
- history of migraine
- pain
- anxiety.

Management of nausea and vomiting requires accurate diagnosis of the cause and knowledge of control pathways and the ways in which anti-emetics work.

Four steps to managing nausea and vomiting

- Identify the cause—this is not always easy because nausea and vomiting are often multifactorial, but it is important because antiemetics are not equally effective against all types of nausea and vomiting. Take an accurate and detailed history, including prescribed and over-the-counter drugs.
- Remove or correct cause if possible—e.g. stop NSAIDs or prescribe laxatives if constipated.
- Treat according to cause—start an appropriate treatment according to the diagnosis (Table 16.2). About 10% of cases require more than one drug. These should preferably be from different groups (but anti-cholinergics antagonize the prokinetic effect of metoclopramide and domperidone). Parenteral administration is frequently more appropriate than oral. See Table 16.2 for recommended drugs.

Table 16.2 Treatment of nausea and vomiting

Cause	First-line drug group	First-line treatment	Second-line treatment	Other treatment
Obstruction	Anticholinergic*/antihistamine	Cyclizine	Hyoscine	Dexamethasone Antihistamine Laxatives
Gastric stasis	Prokinetic	Metoclopramide†	Domperidone	Antacid Dexamethasone
Gastritis	Prokinetic	Metoclopramide†	Cyclizine Domperidone	Antacid Ranitidine Proton-pump inhibitor
Chemical	Dopamine antagonists	Prochlorperazine Haloperidol	Levomepromazine Granisetron/ondansetron/tropisetron Nabilone	Dexamethasone Acupressure (e.g. Sea Band®)
CNS	Antihistamine/anticholinergic	Cyclizine	Hyoscine	Dexamethasone
Psycho-logical Emotional	Anxiolytic	Diazepam	Midazolam Levomepromazine Lorazepam	Reassurance

*Note that anticholinergic side effects can ↑ obstruction.

†At high doses, metoclopramide acts as a 5-HT_3 antagonist.

- Specialist advice should be sought for patients with chemotherapy-induced nausea (see 📖 p.478) or radiotherapy-induced nausea and vomiting or bowel obstruction.
- Review frequently and regularly—if nausea and vomiting persist, change from oral to parenteral administration, ↑ dose, or try drugs from a different therapeutic class. Allow a 24h trial of each intervention before trying another option.

Postoperative nausea and vomiting (PONV)

PONV is a highly undesirable complication of surgery, which can occur in up to 50% of cases. In addition to the consequences already described, severe retching and vomiting postoperatively can put tension on suture lines, cause haematomas below surgical flaps, and ↑ postoperative pain.

Additional risk factors for PONV are as follows.

- Use of inhalation anaesthetics.
- Duration of anaesthesia.
- Use of opioids.
- Use of nitrous oxide.
- Abdominal surgery, notably laparoscopic procedures.
- Perioperative dehydration.

For non-emergency surgery, good preoperative care can ↓ the risk of PONV.

- Identify risk factors and correct or minimize wherever possible.
- Assess unavoidable risk factors:
  - if one risk factor or less, no prophylaxis is required;
  - if two or more, risk factors are present give prophylactic anti-emetics preoperatively;
  - for patients at high risk of PONV, give two antiemetics from different classes preoperatively.

If the patient experiences PONV despite prophylaxis, give an additional antiemetic from a different class.

Drug points

- Avoid metoclopramide in younger patients (≤20 years), because of ↑ risk of dystonic reactions.
- Domperidone does not cross the blood brain–barrier and so is a suitable alternative to metoclopramide in young (♀) patients.
- Long-term metoclopramide, prochlorperazine, and haloperidol can cause extrapyramidal side effects in older patients.
- Levomepromazine should be administered in low doses and titrated cautiously because it is sedative and hypotensive at higher doses.
- Anticholinergics antagonize the prokinetic effect of metoclopramide and domperidone.
- Anticholinergics can cause a 'high' in some patients; avoid in patients with a current or past history of drug misuse.
- Tolerance to opioid-induced nausea and vomiting usually develops after 7–10 days. A prophylactic antiemetic should be used initially and the continued need reviewed after 7–10 days.

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Dyspepsia, peptic ulcer disease, and gastro-oesophageal reflux disease

Dypspesia

- Broad range of symptoms related to dysfunction of the upper GI tract from oesophagus to duodenum. Also described as bad indigestion or heartburn.
- Symptoms include upper abdominal pain or discomfort, acid reflux, fullness, bloating, wind, nausea/vomiting, early satiety, flatulence. It affects 40% of the UK population a year.
- Conditions associated with dyspeptic symptoms include gastro-oesophageal reflux disease (GORD), which accounts for 25–50% of cases, peptic ulcer disease (PUD), gastritis, oesophagitis, gastric, pancreatic, or oesophageal cancer, biliary disease, liver cirrhosis, CRF, Crohn's disease.

GORD

- Acid pepsin or bile reflux into oesophagus from the stomach due to reduced sphincter tone, hiatus hernia, or abnormal oesophageal clearance.
- Symptoms include heartburn, acid regurgitation, and sometimes dysphagia.
- GORD can be complicated by strictures, ulceration, aspiration, Barrett's oesophagus, and adenocarcinoma.

PUD

- Discontinuity/breach in the entire thickness of the gastric or duodenal mucosa of >5mm in diameter with associated inflammation. Commonly involves the stomach (gastric ulcer (GU)), duodenum (duodenal ulcer (DU)), and oesophagus.
- In GU, symptoms of upper abdominal pain are precipitated by eating and weight loss is common. 5% of GU are malignant.
- In DU, symptoms of pain are usually nocturnal, before meals, and are relieved by food or antacids. Weight gain is common.

Pathology of ulcer formation

- Due to imbalance of injurious and protective factors
  - **Injurious factors:** pepsin, bile reflux, gastric acid, *Helicobacter pylori*, rapid gastric emptying, lifestyle (e.g. stress, alcohol, smoking,
  - obesity, fatty diet, chocolate, caffeine,) comorbidities, drugs (e.g. NSAIDs, aspirin, clopidogrel, corticosteroids, SSRIs, calcium-channel antagonists, nitrates, bisphosphonates, theophylline, potassium chloride SR).
  - **Protective factors:** mucus, bicarbonate, prostaglandins, mucosal renewal, mucosal blood flow.
- Acid secretion is under nervous and hormonal control.
- The most common factors contributing to ulcer formation are *H.pylori* and NSAIDs. They are independent risk factors for bleeding and ulceration.

Helicobacter pylori

- *H.pylori* found in gastric antrum predisposes to duodenal ulceration (majority of cases). Infection of proximal stomach predisposes to gastric ulceration.
- Eradication reduces recurrence of gastric and DUs and risk of re-bleeding
- Urea breath test—used to confirm presence of *H.pylori* prior to pre-eradication treatment or post-eradication if symptoms persist or there are complications (e.g. haemorrhage). Proton pump inhibitors (PPIs) should be stopped 2wks prior to test (false positives) and antibacterials 4wks prior to test. Biopsy and stool antigen tests are alternative methods for detecting *H.pylori*.

NSAIDs

- Increased risk during first month of use, elderly, female, high dose/potency, PUD history, smoking, other antiplatelets or anti-coagulants, comorbidities (e.g. rheumatoid arthritis (RA) (5-fold increase), cardiac (2–5-fold increase).
- Corticosteroids alone are insignificant ulcer risk but potentiate NSAIDs.
- SSRIs potentiate NSAIDs and increase risk of bleed 6-fold.
- Topical and E/C NSAIDs can also cause ulceration.
- COX-2 inhibitors have equal efficacy to non-selective NSAIDs but are not without ulcer risk. PPI cover is still recommended in high-risk patients. They are also associated with increased risk of thrombotic events (e.g. MI, stroke).

Referral for endoscopy

- Endoscopy is indicated in patients with the following.
  - Significant upper GI bleed.
  - Dyspepsia associated with alarm symptoms (urgent) defined as any age with any of the following: chronic GI bleeding, weight loss, progressive dysphagia, persistent vomiting, iron-deficiency anaemia (if not on NSAIDs and no menorrhagia), epigastric mass.
- Consider if >55 years old *and* persistent symptoms despite *H.pylori* testing and acid suppression plus one or more of the following: continuing need for NSAIDs, previous GU or surgery, raised risk of anxiety of gastric cancer.

Treatment options

- Lifestyle—e.g reduce alcohol, stop smoking, stress relief, weight loss.
- Drugs.

Antacids/alginates

- Symptomatic relief of PUD especially ulcer dyspepsia and gastro-oesophageal reflux. Not effective in severe disease—do not affect acid secretion.
- Cheap and simple; available OTC. Take when symptoms occur or are expected.

- Some have high sodium content (caution liver disease, hypertension, pregnancy). Aluminum-based—constipating; magnesium-based—diarrhoea. Liquids better than tablets.
- Added ingredients include alginate**s** (Gaviscon®, Rennie®), which form a raft over stomach contents and may help in reflux oesophagitis, or simethicone (Infacol®, Asilone®) which is an antifoaming agent to relieve flatulence.

Proton pump inhibitors (PPIs)

These include lansoprazole, omeprazole, pantoprazole, rabeprazole, esomeprazole. Most effective drugs for PUD/GORD—faster healing rates than H_2 antagonists.

Act by blocking acid pump (H^+/K^+-ATPase) of gastric parietal cell and cause almost total acid suppression for >24h. Inactive pro-drugs with high affinity for acidic environments. Different PPIs bind different sites on the proton pump which may account for variation in potency.

- Indications for oral PPIs.
  - *Short-term treatment*—reflux oesophagitis, benign gastric and duodenal ulcer, *H.pylori* eradication, NSAID-associated ulceration, high-output stomas (e.g. ileostomy). Therapeutic trial in cardiac patients (recommend 2wks and review).
  - *Long-term treatment/prophylaxis*—maintenance therapy with PPIs is usually limited to patients with Barrett's oesophagus, hypersecretory conditions (e.g. Zollinger-Ellison syndrome), complicated oesophagitis (strictures, ulceration, haemorrhage), oesophageal reflux that relapses on stopping therapy. *For these indications, full treatment doses may be needed long term.*
  - High risk factors for GI bleeding that require long-term NSAID use (e.g. the elderly).
  - There is no indication for PPI cover in patients prescribed corticosteroids alone.
- PPIs are generally well tolerated. Haematological effects are rare. There is a reported association with increased risk of hip fracture rates and long-term PPI use. Caution should be taken in severe liver disease, pregnancy, and breastfeeding.
- PPIs may mask the symptoms of gastric cancer and particular care is required in those presenting with 'alarm features'. In such cases gastric malignancy should be excluded before treatment is commenced.
- Co-administration of PPIs and antibacterials increases risk of *Clostridium difficile* 2–3-fold. Review all PPIs on admission, especially if high risk of *C.difficile*-associated diarrhoea (CDAD).
- Drug interactions—PPIs reduce conversion of clopidogrel, a pro-drug, to its active form by competively inhibiting CYP450 2C19. This leads to reduced effectiveness of clopidogrel and increases risk of MI, stroke, etc. The interaction is not seen with H_2 antagonists or pantoprazole which are not metabolized by this enzyme.
- PPIs should be reviewed regularly to ensure that patients are not continued unnecessarily.
- NICE recommends that the least expensive appropriate PPI (within its licensed indications) should be used.

H_2 antagonists

These include ranitidine, cimetidine, nizatidine, famotidine

- Act by blocking histamine receptors on gastric parietal cell, preventing acid secretion into stomach.
- Indications are broadly similar to PPIs, but as PPIs have generally superseded H_2 antagonists the latter are usually only used if PPIs are not tolerated or where drug interactions are an issue.
  - Melaena.
  - Prophylaxis in ITU/hepatic coma/obstetrics.
- More effective than antacids. If once-daily dosing give at night. Side effects rare (<3%). Cimetidine can cause impotence, confusion, and gynaecomastia
- Interactions: CYP450—cimetidine (e.g.warfarin, theophylline, phenytoin); ranitidine (theophylline).
- Dose reduction in renal failure, pregnancy.

Motility enhancers

These include metoclopramide and domperidone. Dopamine receptor antagonists that stimulate gastric emptying and small bowel transit, improve gastro-oesophageal sphincter control, increase oesophageal clearance of refluxed acid. May be of benefit in GORD and in functional dyspepsia unresponsive to PPI/H_2A.

Sucralfate

Complex of aluminium hydroxide and sulphated sucrose which has mucosal protective properties but minimal antacid properties. Used as stress ulcer prophylaxis, GU < DU, chronic gastritis. Side effects are constipation, aluminium toxicity, bezoar formation—care in ITU patients.

Bismuth chelate (tripotassium dicitratobismuthate, Denoltab®)

- Ulcer healing properties comparable to H_2 antagonists, but not in maintaining remission. Used in *H.pylori* regimens—toxic to *H.pylori*.
- Blackens stools and tongue and may accumulate in impaired renal function.
- Counselling required with respect to timing with milk and antacids.

Misoprostol

Synthetic prostaglandin E_1 analogue with antisecretory and protective properties (stimulates mucus and bicarbonate secretion). Promotes GU and DU healing and prophylactic option for NSAID-associated ulcers (when NSAIDs cannot be withdrawn). Side effects—diarrhoea (at dose required), uterine contractions, colic. Take with/after food.

Treatment

H.pylori eradication therapy

- Long-term healing of GU and DU can be achieved by eradicating *H.pylori*. *H.pylori* should be confirmed first.
- Several equally effective regimens available—no large randomized comparable trials; 85% eradication with published regimens.
- 5–20% of patients will not respond because of poor compliance and/or bacterial resistance.

- PPI should usually only be continued if there has been a gastric bleed or perforation.
- 7-day triple-therapy regimes commonly used consisting of a PPI and antibacterials.
- 14-day triple regimes offer higher eradication rate but are offset by more ADRs and poor compliance. 2-week dual regimens are licensed but have poor efficacy and are not recommended.
- Antibacterial-associated CDAD is an uncommon risk.
- Typical regimen—7 days of:
  - omeprazole 20mg bd (any PPI)
  - clarithromycin 500mg bd
  - amoxicillin 1g bd or metronidazole 400mg bd (if penicillin allergic).
- If any of the antibacterials have been used for other infections use the others in combination.
- Resistance to amoxicillin is rare, unlike clarithromycin and metronidazole.
- Tinidazole is an alternative to metronidazole.
- PPI should be continued for a further 3wks if ulcer is large or complicated by haemorrhage or perforation.
- Always give these regimes orally or via a nasogastric tube. Do not start the eradication therapy until the patient can take the full 7-day course by these routes. There is no place in therapy for intravenous *H.pylori* eradication regimens.
- Patient counselling on *H.pylori* eradication should include purpose, dose and frequency, duration (complete the course), avoidance of alcohol with metronidazole (sickness and headache), common side effects. Also advise on general lifestyle changes.

NSAID-induced ulceration

- Withdraw NSAID/COX-2 if possible and substitute with simple analgesia or use lowest dose possible.
- Full-dose PPI or H_2 antagonist for 2 months.
- Eradicate *H.pylori* if present
- Long-term prophylaxis with PPI, misoprostol, or ranitidine 300mg bd if NSAID cannot be withdrawn.
  - Prophylaxis indicated in patients at risk of ulceration on NSAIDs (e.g. elderly, history of PUD) or on other medications with GI risk (e.g. anticoagulants, antiplatelets, etc.)

Complications of PUD

- GI haemorrhage 10% (5–10% morbidity and mortality)
- Perforation—peritonitis 7%
- Pyloric stenosis/obstruction
- Chronic iron-deficiency anaemia
- Penetration—damage to other organs
- Gastric cancer—MALT lymphoma
- Oesophageal—strictures, cancer

Upper GI bleed

- **Haematemesis**—bleed proximal to duodenal–jejunal junction.
  - Large volume, bright red—*rapid, large bleed*
  - Small amount, dark red, 'coffee grounds'—*small bleed altered by gastric acid.*
- **Melaena**—proximal to and including caecum. Black tarry appearance, >60mL blood.
- PUD is most common cause of upper GI bleed—up to 50% due to chronic PUD
- Risk ratio: 3-fold increase if taking NSAIDs.
- Risk of mortality from upper GI bleed assessed via the Rockall score.[1]
- If large bleed or clinical signs of shock, restore blood volume and blood pressure.
- Stop NSAIDs/aspirin, review anticoagulants, SSRIs, aspirin, corticosteroids.
- **Endoscopy** will define cause of bleeding in most patients and therefore is the best treatment. Perform within 24h. Emergency scope and/or surgery candidate if continued bleeding, re-bleed. Consider antibacterial prophylaxis if heart valves etc. Test for *H.pylori*.

Endoscopic therapy

The most effective intervention for those at highest risk of re-bleed and death from PUD.

- Actively bleeding lesion, non-bleeding visible vessels/adherent clot to ulcer:
  - injection sclerotherapy: adrenaline 1:10 000—*vasoconstriction*
  - heater probes/argon plasma gas—*thermal coagulation*
  - endoclips—*ligation*.
- Uncontrolled bleeding/perforation:
  - arterial embolization
  - surgery—under-running (DU), excision/partial gastrectomy (GU).
- Varices—banding, sclerotherapy, trans-intrahepatic portal systemic shunt, balloon tamponade, cyanoacrylate.

Drug therapy

Aims to stabilize clots, and reduce the risk of further bleeding in high-risk patients and the need for surgery. Most deaths from upper GI bleeding are due to respiratory, cardiac, or renal decompensation. Mortality 10–14%.

- PPIs
  - Several reviews have found PPI treatment significantly reduced re-bleeding, surgical interventions and requirement for further endoscopic treatment but it is unclear what effect it has on mortality.

1 Rockall TA *et al.* (1995). Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. *British Medical Journal* **311**; 222–6.

  - No conclusive data on optimum dose of PPI for effectively reducing re-bleeding although national published guidance (SIGN, BNF, and British Society of Gastroenterology recommend high-dose continuous infusion of PPI *post-endoscopic intervention* for major bleeding peptic ulcers (active bleed or non-bleeding visible vessel)—e.g. omeprazole 80mg stat followed by 8mg/h for 72h then po ± *H.pylori* eradication
- Pantoprazole/omeprazole is currently unlicensed for this indication but used in practice. Esomeprazole is licensed.
- There is evidence to show that IV PPI prior to endoscopy has no effect on re-bleeding, need for surgery, or risk of death.
- Ranitidine IV no longer has a place in management.
- Somatostatin and octreotide—poor trial data.
- Tranexamic acid (antifibrinolytic) may be of value in patients with risk of high mortality (Rockall score >3) and confirmed peptic ulcer.
- Can improve clot stability and ↓ risk of re-bleed.
- Terlipressin—variceal bleed (see 📖 p.183).

Further reading

NICE (2004). *Clinical Guideline 17. Dyspepsia: Management of Dyspepsia in Adults in Primary Care.* 🖱 http://www.nice.org.uk/nicemedia/pdf/CG017NICEguideline.pdf

NICE *Gastrointestinal Bleeding: The Management of Acute Upper Gastrointestinal Bleeding* (in progress). 🖱 http://guidance.nice.org.uk/CG/Wave21/1

SIGN (2008). *Guideline 105 Management of Acute Upper and Lower Gastrointestinal Bleeding.* 🖱 http://www.sign.ac.uk/guidelines/fulltext/105/index.html

British Society of Gastroenterology: 🖱 http://www. bsg.org.uk

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Pharmaceutical care in gastrointestinal stoma patients

A GI stoma is a surgically created permanent opening between the GI tract and the skin. These stomas can be temporary or permanent. A stoma may be formed during surgery for cancer, inflammatory bowel disease, or trauma. Patients with GI stomas are susceptible to certain conditions such as ↑ output and dehydration or ↓ output and obstruction, but the presence of a stoma can also influence the choice of drug therapy as it may affect the pharmacokinetics of the chosen formulation.

Dietary advice for stoma patients is provided by specialist dieticians and stoma therapists. Long-term vitamin B_{12} supplementation will be required in patients with an ileostomy because of loss of the terminal ileum.

Management of constipation

Constipation in colostomy patients is usually managed by manipulation of the diet and fluid intake. If drug therapy is considered necessary, its effect should be monitored closely to avoid high output and dehydration. Sodium docusate or balanced osmotic laxatives such as Movicol®/Laxido® are suitable. Lactulose should be avoided as flatulence makes management of the stoma bag difficult.

Laxative enemas and suppositories can be administered via the colostomy but should only be carried out by experienced practitioners. After insertion of the suppository a dressing has to be placed over the stoma to allow the suppository to dissolve; this takes ~20min. The stoma appliance can then be applied. This is a time-consuming method of medication administration.

Constipation is highly unlikely in ileostomy patients, and a lack of output from an ileostomy is usually an indication of obstruction and should be referred for expert management. Laxatives should never be used in ileostomy patients.

Management of a high-output stoma

A normal stoma output will depend on the position of the stoma along the GI tract and the clinical condition of the patient. Colostomy output is usually formed stools. Ileostomy output is more liquid and usually ~1L/day. When output is ↑ the patient will lose different electrolytes depending on the site. Colostomy patients will lose K^+ and fluid; ileostomy patients will lose fluid, Na^+, Mg^{2+}, and possibly Ca^{2+}.

Primary therapy is aimed at removing the cause of the ↑ output such as infection or bacterial overgrowth, but drug therapy should also be reviewed as a possible cause of rapid gut transit. Once any causative factors have been removed or treated, the ongoing output is controlled using loperamide and/or codeine. The dose used depends on the site of the stoma and the output. For colostomy patients a regular dose of loperamide 2mg 1–3 times daily can be effective. For patients with high-output ileostomies or those with a shortened length of gut, loperamide doses of up to 24mg four times daily have been used. This should be under expert supervision. For very-high-output patients a PPI may also be added to reduce the fluid and acid production of the stomach. Not only does

this reduce the volume, but it also reduces the acidity and increases the transit time. Occasionally a high-strength salt solution such as 'St Mark's rehydration solution'[1] or oral rehydration sachets (e.g. Dioralyte®) made to double strength can be used to encourage salt and water reabsorption in the small bowel. The sodium concentration should be >90mmol/L.

Octreotide is not considered effective in management of high-output stomas and is usually considered as a last resort. This should be used in specialist centres only.

High-output ileostomy management

- Expert dietetic advice.
- High-dose loperamide—e.g. 6–24mg four times daily 30min before meals.
- High-dose PPI—e.g. omeprazole 40mg twice daily.
- Codeine phosphate 30–60mg four times daily 30min before meals.
- High-strength salt solution.

Bowel preparation in stoma patients

Bowel preparation is rarely used prior to surgery or procedures now. However, if necessary standard therapies can be used in colostomy patients. Bowel preparation should never be used in ileostomy patients; a clear liquid diet in the 24 hours prior to the procedure is sufficient in these patients.

Medication choice in patients with GI stomas

Where possible modified and slow-release preparations should be avoided as these patients tend to have a reduced GI transit time and the formulation may not have time to release the dose. For ileostomy patients the transit time can vary on a daily basis and variability of absorption can be a problem. Conventional release preparations should be first choice. There is no advantage in using liquid preparations, and occasionally the high sugar or sorbitol content can ↑ the output.

Medication that affects gut transit time should be used with caution and output monitored closely—e.g. metoclopramide, domperidone, or erythromycin in patients with an ileostomy; opiates and ondansetron in patients with a colostomy.

Patients should be counselled on any medication that may colour stool output (e.g. iron preparations) as this can be distressing.

1 http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Q--A/What-is-St-Marks-Electrolyte-Mix-solution/?query=%22St+Mark's%22&rank=100

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