Manual of Medical Therapeutics

24th Edition

Department of Medicine
Washington University School of Medicine
St. Louis, Missouri

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Little, Brown and Company
Boston/Toronto

Twenty-Fourth Edition

Fourth Printing

Library of Congress Catalog Card No. 64-22714

ISBN 0-316-92395-8

Printed in the United States of America

HAL

Preface

The *Manual of Medical Therapeutics* originally was prepared from 1943–1944 by the Department of Internal Medicine of Washington University School of Medicine as a guide for a course in medical therapeutics for fourth-year medical students. Since then the *Manual* has undergone many changes and has enjoyed a much wider distribution among students, house officers, and other physicians and medical professionals.

The emphasis of the *Manual* is on therapeutics, and only those pathophysiologic mechanisms necessary for the understanding of the various medical therapies are discussed. Many topics remain controversial, but we have tried to give the reader a reasonable, conservative, safe approach to such problems. Although the medical therapy outlined here may not represent the only approach to the various disease states discussed, it does reflect the approach employed by the majority of physicians on the staff of Washington University-Barnes Hospital Medical Center. The correct choice of medical therapy will be determined by the individual clinical situation and the medical facilities available.

As in the past, the authors are the chief residents, current fellows, and assistant professors in the Department of Medicine. We, the editors, were chief residents in Medicine in 1982–1983. We are indebted to the many people who helped to bring this edition to publication. Space does not permit the listing of the many members of the Department of Medicine who critically reviewed the manuscripts, but we are most appreciative of their contributions. We are very grateful for the secretarial assistance of Ms. Anita LaTurno, Ms. Karen Roy, Ms. Norma Elder, Ms. Carol Bell, and for the pharmacologic review by Deborah Hahn, Pharm. D. To Ms. Kathleen O'Brien of Little, Brown and Company, we owe thanks for the guidance and understanding that are indispensable in such an effort.

J. W. C.
M. F.

To the **medical house officers** of Washington University School of Medicine, whose concern for excellence in patient care has contributed significantly to the success of the **Manual.**

Contents

1 General Care of the Patient

This chapter is primarily devoted to general topics in therapeutics that are not easily subsumed by traditional medical subspecialties. Although it is beyond the scope of the *Manual* to discuss all the complexities of general patient care, several introductory remarks are in order.

A fundamental principle of patient care is that medical therapy must always be individualized. An approach that is appropriate for one patient may be inappropriate for another with the same disease. Furthermore, the passage of time may dictate varying strategies for the same patient. For example, a stepped-care approach to hypertension is useful as a general guideline; however, the specific antihypertensive program for a diabetic patient with renal impairment may differ markedly from the regimen chosen for a patient with angina or depression.

A second related point is that any medical problem must be viewed in a specific psychosocial context. A therapeutic approach that fails to consider the patient's environmental and emotional background is less likely to succeed than one that takes this background into account. In addition, the management of hospitalized patients is facilitated by the physician's sensitivity to the fact that hospitals may be unfamiliar and stressful for patients. Questions of compliance, family structure, and life-style assume particular importance in the management of outpatients.

I. Hospital orders

A. All orders should be clear, complete, and organized. The importance of writing legibly, especially regarding medications and dosages, cannot be overstated. Initial orders should be written as soon as possible after admission and evaluation and should bear the date, time recorded, and signature of the physician.

B. All orders should be reevaluated at frequent intervals and tailored to the patient's status at that time. If there is a change in an order, the old order should be specifically canceled before the new order is written.

C. Orders for medications to be given prn require careful consideration, especially those concerning the administration of a narcotic. If a prn order for narcotics is written, a definite time limit, not to exceed 48 hours, should be specified.

D. Content and organization of orders. Establishing a routine for writing orders will ensure that no important therapeutic measures will be overlooked. An example of such a routine is as follows:

1. **Admitting diagnosis** and patient's **condition.**
2. Allergies.
3. **Vital signs.** Temperature, pulse, respirations, blood pressure, and specific orders (including orthostatic checks, neurologic signs, and changes for which the physician is to be notified).
4. **Diet.**
5. **Activity** permitted.

6. **Specific nursing instructions.** Intake and output, daily weights, skin or wound care, isolation, postural drainage, etc.
7. **Intravenous fluids,** including composition of fluids and rate of administration.
8. **Medications,** dosage, and frequency and route of administration.
9. **Laboratory tests,** x rays, etc. Open-ended orders, such as "daily CBC," should be avoided to prevent excessive and unnecessary use of diagnostic tests.
10. **Consultations** (e.g., physician specialist, physical therapist, social worker). It is important to specify the reason for the consultation and the questions to which the consultant should direct attention.

II. Drug therapy

A. General comments. Pharmacologic agents should be treated with respect and should only be administered when potential benefits clearly outweigh potential risks. Drugs should not be given merely to satisfy patient expectations.

B. Prescriptions should be written legibly in terms the patient or family can clearly understand. Each prescription should include the patient's name and address, date, name of the drug, dosage, amount dispensed, clear dosage-schedule instructions, number of refills permitted, and signature of the physician. To assist patients in distinguishing among various medications in their possession, it is often helpful to state the reason the drug has been prescribed (e.g., "Hydrochlorothiazide 25 mg, 1 tablet PO daily for high blood pressure").

All prescription containers should be explicitly labeled. Use the generic name whenever possible, write the dosage in metric terms, and never dispense unlimited refills.

C. Adverse drug reactions (i.e., any undesired or unintended drug effects) occur frequently in hospitalized patients and outpatients. The rate increases proportionally to the number of drugs given. Drug reactions may be extensions of known pharmacologic effects (and therefore often dose related), or they may be idiosyncratic. To reduce their frequency:

1. Use as few drugs as possible.
2. Learn the metabolism, routes of execretion, and major adverse effects of the drugs you use. Certain drugs require periodic monitoring of specific laboratory parameters (e.g., gold, penicillamine).
3. Individualize the dose when possible, paying particular attention to the patient's age, size, and metabolic and renal status.
4. Take a careful history of previous drug reactions, and record them conspicuously in the patient's chart.
5. Report unusual drug reactions to the Food and Drug Administration.

D. Drug interactions are complex and embody several different mechanisms (e.g., the interaction between warfarin and phenobarbital). The effect of one drug may potentiate or antagonize the desired or toxic effect of another. Before ordering a new drug, assess the likelihood of a harmful interaction between that drug and those the patient is already receiving. Administer the new drug only if you are reasonably sure that no adverse interaction will occur, or that you will be able to control such an interaction (see P. D. Hansten, *Drug Interactions*. Philadelphia: Lea & Febiger, 1979).

III. Diet and nutrition. This topic, which is so important in general patient care, is discussed in detail in Chap. 11.

IV. Fever

A. General comments. Fever accompanies a wide variety of illnesses, and may be a valuable marker of disease activity. Therefore, under most circumstances, fever should not be treated until its cause is determined. In some cases, however, fever may have deleterious effects, including increased tissue catabolism, dehydration, precipitation or exacerbation of congestive heart failure, delirium, and convulsions (rare in adults). Treatment of fever is indicated when these harmful effects ensue, or when the patient's discomfort is extreme. In addition, heat stroke and malignant hyperthermia are medical emergencies, requiring prompt recognition and treatment (see Chap. 23).

B. Treatment

1. **The antipyretic drugs aspirin** (acetylsalicylic acid) and **acetaminophen** are the treatments of choice in most cases. They are also analgesics and are discussed in detail in secs. **V.B** and **D.**

   In some febrile patients, sporadic use of these agents will cause uncomfortable sweats and chills as the temperature fluctuates. Therefore, these drugs should be given regularly (325–650 mg up to q3–4h) until the underlying disease process has been controlled. Occasional patients are very sensitive to aspirin and may become hypothermic and hypotensive after small doses. Although this is rare, it is wise to use another antipyretic agent in patients whose temperature falls markedly after administration of small doses of aspirin.

2. **Hypothermic blankets** may be effective but require close monitoring of rectal temperatures. Shivering may be a problem. The use of the blanket should be discontinued when the rectal temperature drops to about 38°C, since a further fall usually occurs.

3. **Tepid sponge baths** with water or saline may be used but are less effective in adults than in children.

4. **Ice baths** are reserved for cases of extreme hyperthermia such as encountered in heatstroke (see Chap. 23).

V. Relief of pain

A. General comments. The management of pain must be individualized according to its cause, severity, and chronicity. In addition, the complex interaction between the patient's emotional state, personality, and pain must always be considered, particularly in chronic pain syndromes. Although drugs are the most commonly used therapeutic agents, other nonpharmacologic modalities are frequently appropriate (*Ann. Intern. Med.* 93:588, 1980). Nonopioid preparations should be used whenever possible.

B. Salicylates. Acetylsalicylic acid (aspirin), which has analgesic, antipyretic, and anti-inflammatory effects, is useful for relieving pain originating from many sites. Additional discussion of aspirin appears in the section on rheumatoid arthritis, Chap. 21.

1. **Pharmacologic properties.** The analgesic and anti-inflammatory activity of aspirin probably relates to its ability to inhibit the peripheral production of prostaglandins. Absorbed salicylates are 80% bound to plasma proteins; therefore, higher serum levels of free drug occur in hypoalbuminemia. Salicylates are metabolized by the liver and excreted by the kidneys.

2. **Adverse effects.** Tinnitus, dizziness, and decreased hearing are dose-related side effects. Gastrointestinal distress and GI blood loss (occasionally severe) are frequently encountered. Hypersensitivity reactions (urticaria, bronchospasm, laryngeal edema, hypotension) are uncommon but well recognized (patients with asthma and nasal polyps are especially susceptible).

Small doses of aspirin decrease platelet aggregation and prolong bleeding time. This effect may last up to 1 week. The drug should thus be avoided in patients with bleeding disorders or severe liver disease and in patients taking warfarin. It is desirable to avoid aspirin during the week prior to surgical procedures.

Salicylate overdose is discussed in Chap. 23.

3. **Preparations and dosage**

   a. **Aspirin** is the preparation of choice. For relief of pain, the oral dose is 0.3–1.0 gm (5–15 grains) q4h. Rectal suppositories are available but may be irritating to the mucosa and variably absorbed. The rectal dosage is 0.3–0.6 gm q3–4h.

   b. Other salicylate preparations are discussed in Chap. 21. Recent studies indicate that the newer enteric-coated tablets cause less injury to gastric mucosa than buffered preparations or plain aspirin (*N. Engl. J. Med.* 303:136, 1980).

C. **Other nonsteroidal anti-inflammatory agents.** Except for aspirin, the prostaglandin-inhibiting drugs in this category (e.g., indomethacin, naproxen, tolmetin, ibuprofen, fenoprofen, sulindac) have traditionally been marketed only for the treatment of rheumatologic disorders. However, several compounds in this class are now approved for the treatment of nonrheumatic pain (e.g., zomepirac sodium, naproxen sodium). Some of these drugs compare favorably with codeine-aspirin or codeine-acetaminophen combinations in the treatment of postoperative or dental pain. There are few data to indicate how the nonsteroidal, anti-inflammatory agents compare with each other as analgesics. They are a reasonable choice when aspirin or acetaminophen are inadequate and opioids are to be avoided. They are discussed in detail in Chap. 21.

D. **Para-aminophenol derivatives. Acetaminophen** has analgesic and antipyretic actions but does not have anti-inflammatory properties. **Phenacetin,** whose major metabolite is acetaminophen, is a constituent in several analgesic combinations, but is generally not used as an isolated preparation. The therapeutic actions of these two drugs are essentially identical.

1. **Side effects and toxicity.** The principal advantages of acetaminophen over aspirin are the lack of gastric toxicity and the absence of effects on platelet aggregation. The most serious toxicity of acetaminophen is hepatic. Acute overdosage with 10–15 gm may cause fatal hepatic necrosis; management of overdose is discussed in Chap. 23. Toxic hepatitis may also occur in patients chronically ingesting several grams a day. Thrombocytopenia is a rare side effect.

   Acute or chronic overdosage with phenacetin may cause hemolytic anemia (especially in patients with glucose 6-phosphate dehydrogenase deficiency) and methemoglobinemia, but these effects are rarely seen with acetaminophen. Chronic phenacetin ingestion of 1–3 gm daily for several years may result in "**analgesic nephropathy,**" which is characterized by interstitial inflammation and papillary necrosis. Progressive renal insufficiency may ensue. This syndrome occurs particularly when combinations of phenacetin and aspirin are taken chronically. Acetaminophen, on the other hand, is not firmly established as a nephrotoxin.

2. **Preparations and dosage. Acetaminophen** is the preparation of choice. For relief of pain, the oral dosage (in tablets, capsules, or elixir) is 325–650 mg q4–6h. Rectal suppositories are also available.

E. **Opioid analgesics**

1. **General comments.** In this discussion, the term *opioid* refers to a series of naturally occurring and synthetic drugs that have pharmacologic, but not

necessarily structural, similarities to opium or morphine. These drugs are primarily employed as analgesics, but they are also used to suppress severe cough and diarrhea. Common errors that occur with the use of opioids include underestimation of the amount of drug required for pain relief, overestimation of the duration of action, and possibly an exaggerated estimation of the dangers of addiction for medical inpatients.

2. **Precautions**

   a. **Opioids should be used only when other drugs or physical measures will not provide relief of pain.** One should give the smallest doses that provide adequate analgesia. **Tolerance** to the analgesic effects of opioids occurs with continued use (i.e., increasing doses are required to maintain the same effect).

   b. **Physical dependence** may occur with any of the opioid preparations. In most patients, 2 weeks or longer is required for physiologic addiction to develop. However, withdrawal symptoms may be precipitated by the opioid antagonist naloxone after only several days of opioid use. The hazard of addiction should not preclude long-term administration of these drugs to patients with terminal illnesses.

   c. **Opioids should be used with extreme caution** in patients with hypothyroidism, Addison's disease, hypopituitarism, anemia, reduced blood volume, head trauma, asthma, severe malnutrition, or debilitation. In patients with increased intracranial pressure, opioids may further elevate cerebrospinal fluid pressure. Since these drugs are metabolized in the liver, patients with hepatic disease may be inordinately sensitive to the usual dosage. Phenothiazines, antidepressants, and CNS depressant drugs may markedly potentiate the adverse effects of opioids. If it becomes necessary to use opioids in any of these settings, very small doses should be used initially.

   d. **Opioids are contraindicated** in certain acute disease states (e.g., suspected surgical abdomen) in which the pattern and degree of pain are important diagnostic signs. Similarly, their administration to patients with acute head injuries may complicate accurate assessment of neurologic changes.

   e. **Opioid-induced vomiting** may often be avoided by keeping the patient recumbent.

   f. **The opioid antagonist naloxone,** a short-acting semisynthetic congener of morphine, is used to counteract the symptoms of excess doses of opioids (particularly hypotension and depression of respiration and consciousness). The management of opioid overdose is discussed in Chap. 23.

3. **Adverse and toxic effects.** Most of the adverse effects of opioids are extensions of their known pharmacologic actions. There are few differences in the adverse effects of various opioids when given in equianalgesic doses, but an individual patient will usually tolerate some preparations better than others.

   a. **Central nervous system effects** include sedation, mood alteration, euphoria, and pupillary constriction. Nausea and vomiting may be particularly troublesome, even with therapeutic doses.

   b. **Respiratory depression** occurs in direct proportion to the dose. Therapeutic doses diminish both tidal volume and respiratory rate. Therefore, opioids should be used cautiously, if at all, in patients with pulmonary insufficiency and asthma.

   c. **Cardiovascular effects** include peripheral vasodilation, hypotension (especially orthostatic), and circulatory collapse.

d. **Gastrointestinal effects** include a decrease in propulsive peristalsis in the large and small bowel and an increase in smooth muscle and sphincter tone. Opioids may precipitate toxic megacolon in patients with severe ulcerative colitis.

e. **Biliary tract spasm** may be induced, and patients with biliary colic may have an increase in pain. Elevation of serum amylase may result from this mechanism.

f. **Genitourinary effects** include increases in ureter, bladder, and sphincter tone. Urinary retention may be provoked, especially in patients with prostatic hypertrophy.

g. **Allergic reactions** are rare and include urticaria and other rashes and anaphylaxis, which may account for episodes of sudden death among addicts.

4. **Clinical use.** When oral opioid preparations are necessary for short-term administration, codeine or oxycodone are the drugs of choice (generally in combination with aspirin or acetaminophen). In situations necessitating parenteral drug administration, we use meperidine or morphine. Oral morphine and hydromorphone are usually given to cancer patients with chronic severe pain (see Chap. 17).

   Hydroxyzine hydrochloride, 25–50 mg IM, potentiates the effect of a given dose of an opioid and may reduce the frequency of IM injections. It also has antiemetic properties.

5. **Selected preparations and dosage.** Information concerning the relative potency of these drugs is given in Table 1-1.

   a. **Morphine sulfate.** The usual effective IM or SQ dose is 10 mg/70 kg of body weight, although this may vary with the extent of previous administration. In some patients, 5 mg may afford excellent analgesia, while others may require up to 15 mg. The duration of action is roughly 4–5 hours. Morphine may be given cautiously IV (primarily in the setting of acute myocardial infarction or acute pulmonary edema). The usual IV dose is 2–4 mg given slowly over 5 minutes.

   b. **Codeine** is dispensed as water-soluble sulfate and phosphate salts. Analgesia is enhanced when codeine is combined with aspirin or acetaminophen. The usual analgesic dosage is 30–60 mg PO, IM, or SQ q4–6h. Codeine is also widely used as a **cough suppressant** in a dosage of 15–30 mg PO q4–6h.

   c. **Oxycodone** is a semisynthetic opioid. In the United States, oxycodone is marketed only for oral use, in combination with acetaminophen or aspirin. The usual dosage is 5 mg PO q6h.

   d. **Hydromorphone** is a semisynthetic derivative of morphine. The usual dosages are 2–4 mg PO q4–6h or 1–4 mg IM or SQ q4–6h. One should generally start with the lower doses. The drug may also be given IV (over several minutes) and as 3-mg rectal suppositories.

   e. **Meperidine** is a synthetic opioid. Its duration of action (2–4 hours) is shorter than that of morphine. Meperidine causes less constipation and biliary spasm than a comparable dose of morphine. Adverse effects are otherwise similar to those of morphine except that toxic doses are more likely to cause seizures. The usual dosage is 50–150 mg PO, IM, or SQ q3–4h; IM or SQ injections are locally irritating.

   f. **Propoxyphene** is structurally related to methadone. In standard doses, its analgesic potency may be no better than that of aspirin, although this varies among individuals. Accordingly, side effects at the usual clinical doses tend to be minimal. The usual oral dosage is 65 mg of propoxyphene

Table 1-1. Analgesic potency of selected opioid drugs

Drug	Oral-parenteral potency ratio[a]	Potency relative to morphine (for equal parenteral doses)[b]
Morphine	1 : 6	1.0
Codeine	2 : 3	0.1
Oxycodone	1 : 2	1.0
Hydromorphone	1 : 5	6.0
Meperidine	1 : 3	0.15
Pentazocine	1 : 3	0.25

[a] For example, morphine is 6 times more potent parenterally than orally.
[b] For example, hydromorphone is 6 times more potent than an equal dose of morphine, when given parenterally.
Source: The figures in this table are approximations based on a variety of references.

hydrochloride or 100 mg of propoxyphene napsylate q4–6h. Combinations of propoxyphene and aspirin or acetaminophen are more effective than either agent alone.

g. **Pentazocine** is a synthetic drug with both opioid agonist and antagonist actions. Its antagonist effect is demonstrated by its ability to induce withdrawal symptoms in chronic users of other opioids. However, the drug is itself antagonized by naloxone. Its unique adverse effects, in contrast to morphine, include hypertension, tachycardia, and hallucinations. Pentazocine originally was considered to have minimal addictive potential, but clinical experience has not supported this contention. Accordingly, the drug confers little advantage over other agents. The usual dosage is 50 mg PO or 30 mg IM q3–4h; SQ administration should be avoided if possible because of local tissue irritation.

Psychoactive Drug Therapy

I. Sedative-hypnotic and antianxiety drugs

A. General comments. These drugs are among the most widely prescribed medications today, primarily because of the popularity of the benzodiazepines. However, there is reason to believe that the use of these drugs is excessive. Physicians should never prescribe them without fully investigating the source of a patient's anxiety or insomnia.

It is becoming increasingly appreciated that **insomnia** is a symptom that may actually reflect a variety of underlying medical or psychiatric disorders. For example, sleep disturbances may occur secondary to depression, and specific treatment should be directed toward the latter condition. When insomnia occurs as an isolated symptom, behavioral or relaxation techniques should be attempted before resorting to drug therapy.

In general, hypnotics lose their effectiveness within relatively short periods of time. Therefore, their use should be limited to brief periods of a few days or weeks. **Ongoing refills should not be made available.** Many of these medications may interfere with daytime mental functions, and they interact unfavorably with alcohol and other CNS depressants. Most hypnotics change the duration of various sleep stages (e.g., suppress REM sleep), and patients are subject to rebound insomnia when they are discontinued. There is a potential for

psychologic and physical dependence with most of these drugs, including the benzodiazepines.

Similarly, use of these drugs for **anxiety** should generally be limited to brief periods of time corresponding to transient anxiety-provoking situations. Patients with chronic nonspecific anxiety rarely experience sustained improvement in symptoms with chronic tranquilizer use; rather, they become entrapped in a situation of psychologic and physical dependence. The management of these patients requires considerable effort by physicians and allied health professionals. Counseling and behavioral techniques may be helpful.

Sedative-hypnotic and antianxiety drugs should be used cautiously and in lower dosage in elderly patients (who may be very sensitive to their effects) and in patients with hepatic insufficiency, pulmonary disease, heart failure, anemia, myxedema, and high fever.

B. Benzodiazepines

1. **Pharmacologic properties and adverse effects.** These drugs have similar actions but differing pharmacokinetics. They are metabolized primarily in the liver and must be used cautiously in patients with hepatic disease. Concomitant administration of cimetidine may increase the therapeutic effect of benzodiazepines. Adverse reactions include excessive drowsiness, paradoxical hyperexcited state, and mental impairment. Withdrawal symptoms occur after prolonged use, necessitating gradual discontinuance of the drug. One should not confuse withdrawal symptoms with an increase in the underlying anxiety itself.

2. **Selected agents**

   a. **Diazepam.** The dosage is 2–10 mg PO tid prn. The half-life is 20–50 hours; metabolites are also active and are slowly degraded into inactive products.

   b. **Chlordiazepoxide.** The dosage is 10–25 mg PO tid prn. The half-life is 6–30 hours; metabolites are also active and slowly degraded.

   c. **Oxazepam.** The dosage is 10–15 mg PO tid prn. The half-life is 3–21 hours; metabolites are inactive. Thus, less accumulation of active drug occurs with prolonged use, as compared with diazepam and chlordiazepoxide.

   d. **Lorazepam.** The dosage is 0.5–1.0 mg PO tid prn. The half-life is 10–20 hours; metabolites are inactive.

   e. **Flurazepam** is specifically marketed for insomnia, although it may be no more effective for this purpose than other benzodiazepines. The dosage is 15–30 mg PO hs. Metabolism is rapid, but the half-lives of active metabolites are 50–100 hours.

C. Barbiturates

1. **Pharmacologic properties.** Both long-acting and short-acting preparations are available. Long-acting barbiturates such as phenobarbital are metabolized slowly in the liver and are cleared primarily by the kidney (partially as unchanged drug). Short-acting preparations (e.g., secobarbital and pentobarbital) are metabolized primarily by the liver and depend minimally on renal excretion. Barbiturates should be given parenterally only in emergency situations such as status epilepticus. The barbiturates have a relatively poor therapeutic index (i.e., a low ratio of toxic to therapeutic dose). Thus, they have been generally supplanted by the safer benzodiazepines for the treatment of anxiety and insomnia.

2. **Adverse effects.** Barbiturates are CNS depressants and accordingly cause drowsiness and mental impairment (but no analgesia). These effects are

additive with other CNS depressants, including alcohol. Barbiturates may paradoxically cause excitement on occasion.

Barbiturates cause **respiratory depression** and are thus contraindicated in patients with pulmonary disease. The induction of the hepatic microsomal system by barbiturates necessitates dosage adjustments of hepatically metabolized drugs such as warfarin. Other adverse effects include hypersensitivity reactions (cutaneous and systemic) and exacerbation of acute intermittent porphyria. These drugs should be avoided in patients with hepatic disease.

3. **Tolerance** to the effects of barbiturates occurs with continued use. **Physical addiction** is a danger when large or even therapeutic doses are taken for more than several weeks. When barbiturates are withdrawn from addicted patients, the decrement in dosage should not exceed the equivalent of 30 mg daily of phenobarbital, to prevent such serious reactions as delirium and seizures. (See T. P. Hackett and N. H. Cassem (eds.), *Massachusetts General Hospital Handbook of General Hospital Psychiatry*. St. Louis: Mosby, 1978.)

4. **Acute barbiturate overdose** or poisoning is a medical emergency (see Chap. 23).

5. **Preparations**

   a. **Long-acting.** Effects are noticeable in 30–45 minutes and last 4–8 hours. Hangovers are frequent. The dosage of phenobarbital is 100–200 mg at bedtime. For daytime sedation, the dosage is 15–30 mg tid prn, but phenobarbital is rarely indicated for this use.

   b. **Short-acting.** Onset of action is 15–30 minutes, and the effects last 2–4 hours. Hangovers are less common. Oral hypnotic doses for pentobarbital, secobarbital, and amobarbital are 100–200 mg hs. These drugs are not used for daytime sedation.

D. **Chloral hydrate** is a rapidly effective hypnotic that seldom produces excitement or hangover and has minimal effect on sleep stages. Sleep usually begins in 15–30 minutes and lasts 5–8 hours. The drug is detoxified chiefly by the liver, and products are excreted by the kidneys. It should not be given to patients with severe hepatic, renal, or cardiac disease. Side effects include gastric irritation, rare skin reactions, and potentiation of the anticoagulant effect of warfarin. Tolerance, addiction, and withdrawal syndromes can be seen with chronic ingestion. Toxic doses cause CNS and respiratory depression. A reduction product, trichloroethanol, may give a positive result for urine sugar with Clinitest tablets. The usual hypnotic dose is 0.5–1.0 gm hs. Single doses or daily dosage should not exceed 2 gm.

E. **Antihistamines**

1. **Diphenhydramine,** though not marketed as a sedative, may be used for this purpose. Its side effects are principally anticholinergic in nature. The drug is a good choice when a combination of antipruritic and sedative activity is desired. The dosage is 25–50 mg qid prn or 25–50 mg hs.

2. **Hydroxyzine** is a compound with antihistaminic effects. It is marketed specifically as an antianxiety and antipruritic agent. The drug has sedative and antiemetic effects. Oral preparations include hydroxyzine pamoate and hydroxyzine hydrochloride; the dosage is 25–50 mg qid prn or 25–50 mg hs. Hydroxyzine hydrochloride is also available as an IM preparation. It is often used in combination with meperidine to potentiate the latter's analgesic effect and to provide antiemetic and sedative effects. The usual dosage is 25–50 mg IM q3–4h.

F. **Other agents.** Ethchlorvynol, glutethimide, meprobamate, and methyprylon

were all commonly used sedatives until recently. They are relatively toxic compared with the benzodiazepines and are thus not recommended for routine use.

Paraldehyde also has few indications. It has generally been replaced by the benzodiazepines in the treatment of alcohol withdrawal. This drug may still have a role in the treatment of status epilepticus (see Chap. 22).

II. Phenothiazines and related antipsychotic drugs

A. General comments. These drugs, of which chlorpromazine is the prototype, are commonly used in psychiatric disorders (especially psychoses) and for treatment of nausea and vomiting. Although several dozen compounds are available, the clinician is best served by becoming familiar with a few representative drugs, since they differ widely in their potency and side effects. Addiction does not occur, and overdoses rarely result in death.

B. Pharmacologic properties. Although the exact mechanism of action is unknown, the antipsychotic and CNS effects are probably related to dopamine antagonism. These drugs also have anticholinergic, antihistaminic, and antiadrenergic activity in varying degrees. Absorption from the GI tract is rapid but erratic; IM injections yield more bioavailable drug. Their half-lives in plasma are generally in the range of 10–20 hours. Phenothiazines are metabolized by the liver, and metabolites (which are mostly inactive) are excreted in the urine and bile. These drugs should be given cautiously to patients with hepatic disease.

C. Adverse reactions. The toxic effects of these agents include those that are extensions of their CNS activity (i.e., sedation, autonomic effects, and extrapyramidal reactions) and those that are idiosyncratic. In general, for the lower-potency preparations such as chlorpromazine (i.e., those that require large doses for a therapeutic effect), autonomic and sedative effects outweigh extrapyramidal reactions; the reverse is true for the high-potency drugs such as haloperidol (see Table 1-2).

1. **Hypotension,** often orthostatic, may occasionally be acute and severe after IM doses.
2. **Anticholinergic effects** include dry mouth, blurred vision, urinary retention, constipation, and tachycardia.
3. **Extrapyramidal reactions**
   a. **Parkinsonian reactions,** which usually occur early in therapy, include the tremor, bradykinesia, rigidity, and abnormalities of gait and posture seen in idiopathic parkinsonism. Treatment with antiparkinsonian drugs, such as benztropine or trihexyphenidyl, may be required if these reactions occur.
   b. **Akathisia,** another early side effect, is a sense of motor restlessness in which the patient has a constant need to move about. It should not be confused with a worsening of the underlying psychiatric disorder.
   c. **Acute dystonic reactions** may occur shortly after starting therapy and are characterized by torticollis, opisthotonos, tics, grimacing, dysarthria, and oculogyric crisis. For severe reactions, diphenhydramine, 25–50 mg PO, IM, or IV, or benztropine, 1–2 mg PO, IM, or IV, are usually effective.
   d. **Tardive dyskinesia** is a late side effect (occurring after months to years of therapy) characterized by involuntary movements of the tongue, lips, jaw, and extremities. The syndrome may emerge during phenothiazine therapy and is frequently unmasked when the dosage is lowered; it may persist indefinitely after the drug is stopped.
4. **Skin reactions** include photosensitivity, urticaria, and maculopapular rashes.
5. **Cholestatic jaundice,** which occurs most commonly with chlorpromazine, is