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Central nervous system (including peripheral analgesics)

This chapter discusses oral analgesic/antipyretic drugs, sedatives, and stimulants. Sedative and stimulant drugs act directly on receptors in various parts of the brain while OTC internal analgesics first react in the periphery to inhibit the synthesis of a series of compounds known as prostaglandins. All of the OTC analgesics have an antipyretic effect, reducing an elevated body temperature by acting on the hypothalamus in the brain. The brain and spinal cord make up the central nervous system (CNS).

Many of the effects of prostaglandins are produced locally in tissues, but some of their analgesic effects may be mediated by stimulating neurons in the peripheral nervous system. Nerves from the peripheral nervous system propagate signals to the spinal cord that reach the brain via afferent nerve pathways. Transmission of nerve impulses from the brain and spinal cord to the peripheral tissues occurs via efferent nerve fibers.

Oral OTC analgesic drugs do not identify the cause of pain nor do they correct it; they merely prevent or relieve mild to moderate pain. External analgesics are drugs applied topically to the skin or mucous membranes to block or prevent transmission from the peripheral nervous system. External OTC analgesics are discussed separately Chapters 7 (topical OTC oral cavity products) and 8 (topical OTC drugs for dermatological conditions).

OTC analgesics include acetaminophen and several drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin, other salicylate drugs, ibuprofen, naproxen sodium, and ketoprofen. All of the drugs produce analgesic and antipyretic effects, but acetaminophen has little to no effect on inflammation.

The FDA has approved caffeine as a monograph analgesic adjuvant. An adjuvant is a drug that does not have any analgesic activity but if combined with an approved analgesic provides greater pain relief than the analgesic by itself.¹

Acetaminophen, aspirin, and ibuprofen may be used for all types of headache including migraine headache. Manufacturers of products labeled exclusively for migraine pain obtained FDA approval by submitting additional data. Directions for use of these products differs from their use as ordinary analgesic/antipyretic products.²

Oral analgesics

Acetaminophen

Acetaminophen is one of the most widely used analgesics in the USA. It is used OTC for all age groups over the age of 2 years and is prescribed by healthcare professionals for those under 2 years of age. It is the analgesic least likely to cause GI symptoms, gastric irritation, GI bleeding, and ulcers, and it does not affect blood platelets.

Acetaminophen is metabolized by the liver and is associated with liver toxicity and death. This risk is increased if the use of acetaminophen involves high daily doses, a long period of use, or the ingestion of three or more alcohol beverages per day. Accidental ingestions by children or adults require immediate treatment, even if there are no immediate symptoms of toxicity.

Drug category and indications for use

Acetaminophen is an analgesic and antipyretic. It may be used to reduce fevers and provide temporary relief for minor aches and pains caused by the common cold, sore throat, toothache, headache, muscular aches and pain, premenstrual and menstrual cramps (dysmenorrhea), and pain associated with arthritis.¹

Monograph ingredient

Acetaminophen.

Mode of action

Acetaminophen is a weak inhibitor of prostaglandin synthesis in the periphery but has a more pronounced effect in the brain; its full mechanism of action remains uncertain. It has no true anti-inflammatory activity as NSAIDs have, but it is recommended as a primary drug for relieving mild to moderate arthritic pain. Two basic reasons for its use are that much of the pain associated with osteoarthritis is not from an inflammatory process and its safety profile for those over the age of 60 years is much better than that of the NSAIDs.³

Warnings and precautions

Adults and children over 12 years of age should not exceed the recommended dose of 4 g per 24 hours because severe liver damage may occur at higher dosage. Acetaminophen should not be used without consulting a physician if

an individual has liver disease. If the individual consumes three or more alcoholic drinks every day, a physician should be consulted before taking this product. OTC acetaminophen should not be used with any other drugs, prescription or nonprescription, containing acetaminophen. A physician or pharmacist should be consulted by anyone unsure of the content of other drugs they are taking.^{4,5}

Acetaminophen should not be used for more than 10 days for temporary relief of pain and for not more than 3 days if used for fever. If fever occurs or swelling or redness occurs at the site of pain, a physician should be consulted. Products labeled for sore throat pain are limited to 2 days of use. If the pain worsens or a fever develops, a physician should be consulted.^{1,5,6}

Children under 12 years of age should not take more than five doses of acetaminophen in a 24 hour period because it could cause severe liver damage. The drug should not be used without consulting a physician if the child has liver damage or if the child is taking any other product that contains acetaminophen. If the caregiver is unsure of the content of other drugs the child is taking, a physician or pharmacist should be consulted.

Acetaminophen products for children 2 to 12 years of age should not be labeled for use of muscle aches and pains, premenstrual or menstrual cramps, or arthritis.^{5,6}

The FDA issued a final monograph for labeling of all internal analgesics on April 29, 2009. Even though acetaminophen does not affect blood platelets, all acetaminophen products must contain a warning by April 2010 that a physician or pharmacist should be consulted if the individual is taking warfarin.⁶ Maximum doses of acetaminophen taken for 1 week or more increase the anticoagulant effect of warfarin by influencing its pharmacokinetics.⁷

NOTE: All these warnings about acetaminophen are required to be on the product's label when acetaminophen is combined in cough/cold products, sinus pain relief products, premenstrual and menstrual pain relief products, or sedative products.^{5,6}

In June 2009, an FDA Advisory Committee recommended stronger warnings or perhaps removal of acetaminophen from many combination prescription products because of accidental overdoses.⁷ These recommendations may extend to nonprescription products in the future, especially allergy/cough/cold products. Such a change would affect many products on the market and may result in formulation changes.

Recommended dose

Adults and children over 12 may take one or two 325 mg (regular strength) or 500 mg tablets (extra strength) every 4 to 6 hours, but should not exceed 4000 mg in 24 hours; sustained release acetaminophen is available as 650 mg tablets and one to two tablets may be taken every 8 hours but must be swallowed, not chewed or crushed.^{5,6}

Table 5.1 Recommended doses of acetaminophen syrup or suspension (160 mg per teaspoon (tsp) or 5 mL) for children 2–12 years of age

Weight (lbs)	Weight (kg)	Age (years)	Oral dose ^a
Under 24	Under 11	Under 2	Consult doctor
24–35	11–16	2–3	1 tsp or 5 mL (160 mg)
36–47	16.3–21.3	4–5	1.5 tsp or 7.5 mL (240 mg)
48–59	21.8–26.8	6–8	2 tsp or 10 mL (320 mg)
60–71	27.2–32.2	8–10	2.5 tsp or 12.5 mL (400 mg)
72–95	32.7–43.2	11–12	3 tsp or 15 mL (480 mg)

^aDoses should be measured only with the measuring device enclosed in the package.

The recommended doses of acetaminophen syrup or suspension for children between the ages of 2 and 12 years are given in table 5.1 and for concentrated infant acetaminophen drops in table 5.2.

Concentrated infants drops contain more acetaminophen per milliliter than do syrup or suspension formulations and should only be measured with the dropper that is packaged with the container. Failure to use the appropriate measuring device may result in improper doses and is a frequent cause of overdoses when the concentrated infant drops are used.

Products

Tylenol Regular Strength, Tylenol Extra Strength, Tylenol 8 hour, Tylenol Arthritis, FEVERALL Suppositories, and Panadol.

NOTE: Tylenol 8 hour may be used in children over 12 years of age and Tylenol Arthritis may be use in individuals over 18 years of age. Both contain the same formula of sustained release acetaminophen, but arthritis products may not be labeled for use in individuals under 18 years of age. Arthritis that occurs in a child or adolescent requires physician treatment, not self-care.

Table 5.2 Recommended doses for concentrated acetaminophen infant drops (concentration, 80 mg in 0.8 mL; 1 dropperful is 0.8 mL)

Weight (lbs)	Weight (kg)	Age (years)	Dose
Under 24	Under 11	Under 2	Consult doctor
24–35	11–16	2–3	1.6 mL (use two dropperful doses of 0.8 mL) (160 mg)

Nonsteroidal anti-inflammatory analgesic/antipyretic drugs

Monograph drugs

Aspirin (acetylsalicylic acid), carbaspirin calcium, choline salicylate, magnesium salicylate, sodium salicylate, ibuprofen, naproxen sodium, and ketoprofen are all classified as NSAIDs.

Drug category and indications for use

NSAIDs may be used to reduce fever and provide temporary relief for minor aches and pains caused by the common cold, sore throat, headache, muscular aches and pain, backache, premenstrual and menstrual cramps (dysmenorrhea), and pain associated with arthritis.^{1,5,6}

Low-dose aspirin (81 mg per day) may be recommended by a physician to prevent the aggregation of blood platelets to reduce the risk of heart attacks and strokes in certain individuals.

Mode of action

Aspirin and the other salicylates combine with cyclo-oxygenase enzymes (COX-1 and COX-2), which are responsible for the first step in the formation of prostaglandins and thromboxanes from arachidonic acid in the periphery. Prostaglandins are produced in the inflammatory response and are involved in the production of pain, especially pain associated with headache and premenstrual and menstrual pain. The anti-inflammatory effect of aspirin and salicylates derives from their ability to inhibiting prostaglandin synthesis. Consequently, they are known as nonsteroidal anti-inflammatory drugs, NSAIDs.³

Prostaglandin E₂ (PGE₂) produced in the periphery increases cyclic adenosine monophosphate (cyclic AMP), which causes the hypothalamus to increase body temperature. Aspirin and the other NSAIDs inhibit PGE₂ synthesis, thus having an antipyretic effect.³

Prostaglandin H₂ is converted to thromboxanes, which are involved in platelet aggregation to stop bleeding. Because aspirin, but not other salicylates, binds irreversibly to the acetyl site of COX-1, it is used for its anticoagulant activity in individuals who are at risk for heart attacks and strokes that are caused by blood clots. Individuals should consult their physician before using aspirin for these cardiovascular uses.^{1,3,5-8}

Aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, sodium salicylate, and ibuprofen administered in recommended doses have the same efficacy as analgesics and antipyretics.^{1,5}

Warnings and precautions

Individuals allergic to aspirin or any other pain or fever relief drug should not take the drug as they may experience hives, asthma (wheezing), facial swelling, or shock. The drug should be stopped immediately if any of these symptoms occur and a physician should be contacted.^{1,5,6}

Children and teenagers should not use this drug if they have recovered, or are recovering, from flu or chickenpox because they may develop Reye's syndrome, a serious condition associated with the use of aspirin and salicylates.^{5,6,9} Reye's syndrome occurs usually after a viral infection such as chickenpox or flu. Symptoms include persistent vomiting, fatigue, and confusion, and the syndrome may progress to convulsions, unconsciousness, and death. There is an increase in intracranial pressure and increased fatty deposits in the liver and other organs. Immediate treatment minimizes the residual effects of this condition.¹⁰

All NSAIDs may cause stomach bleeding and the risk of this event is greater if individuals are over 60 years of age, have bleeding problems, peptic ulcer disease, diabetes, gout, or arthritis, or if the individual is taking an anticoagulant drug (blood thinner), steroids, or any other drugs containing NSAIDs. Consuming three or more alcoholic beverages a day, taking more than the recommended dose, or taking the drug for a longer period of time than recommended increases the risk of bleeding.^{5,6}

The appearance of blood or occult blood in any vomit or stool may indicate stomach bleeding, and a physician should be consulted immediately. If an individual experiences stomach pain or ringing in the ears, a physician should be consulted.^{5,6}

If NSAIDs do not relieve pain within 10 days, or fever within 3 days, a physician should be consulted. If the symptoms worsen or redness develops in the area of the pain, a physician should be consulted. If the product is labeled for sore throat pain, its use should be limited to 2 days.^{1,5,6}

NSAIDs should not be used during the last 3 months of pregnancy unless directed by a physician because it may cause problems for the unborn child and complications during delivery.^{1,5}

Aspirin should not be used to reduce the risk of a heart attack unless advised to do so by a physician.⁵

If a magnesium salicylate product has more than 50 milliequivalents of magnesium in the recommended daily dose, it should not be used by individuals with kidney disease without consulting a physician.¹

If individuals have diabetes, high blood pressure, kidney disease or take a diuretic drug, a physician should be consulted before using any NSAID. NSAIDs may inhibit prostaglandins that produce vasodilatation of blood vessels in the kidney, resulting in vasoconstriction and causing an increase in blood pressure, further compromising kidney function in individuals who have kidney disease.^{6,11,12}

There are two special warnings for ibuprofen in addition to all the other NSAIDs warnings.

Special ibuprofen warning for concomitant use with low-dose aspirin (81 mg). There is competitive action between ibuprofen and aspirin for the

acetyl-binding site of cyclo-oxygenase when both drugs are administered together. Since this is the site where aspirin acts to prevent platelet aggregation for its cardiovascular effect, its effectiveness will be reduced. If an individual uses both drugs, aspirin should be administered 8 hours after ibuprofen.¹³ There is little evidence that naproxen sodium and ketoprofen might have the same effect.

Special ibuprofen warning for migraine headache use. Individuals should not use ibuprofen for a migraine headache if a physician has never diagnosed their problem as a migraine headache. If the headache differs from previous migraine headaches, is the worst headache of their life, is accompanied by a fever and stiff neck, or has occurred after a head injury, a physician should be consulted. If the headache is caused by bending, coughing, or exertion, occurs daily, or is accompanied by vomiting, a physician should be consulted before using ibuprofen. Ibuprofen is not recommended for treating migraine headaches in individuals under 18 years of age unless a recommendation was made by a physician.¹⁴

Recommended dose

Aspirin for pain or fever relief. Adults and children over 12 years of age may take two tablets of either 325 mg (regular strength) or 500 mg (extra strength) aspirin per dose every 4 to 6 hours, not exceeding 12 tablets within 24 hours. Although the monograph permits aspirin use in children under 12 years of age, most healthcare professionals do not recommend its use; acetaminophen is the preferred drug in children under 12 years of age.^{1,6}

Aspirin for reduction of cardiovascular risk. The dose of aspirin recommended is 81 mg per day for most individuals (a ‘baby’ aspirin), but this use should be discussed with a physician. Doses higher than 81 mg (325 to 500 mg) may be recommended by a physician for certain individuals.

Salicylate drugs. Dose recommendations are given in table 5.3.

Table 5.3 Recommended adult doses of analgesic/antipyretic salicylate drugs (maximum 4 times a day)

Drug	Adult dose (mg)
Aspirin	325–1000
Carbaspirin calcium	414–828
Choline salicylate	435–870
Sodium salicylate	250–650
Magnesium salicylate	325–650

Table 5.4 Recommended doses of ibuprofen for children under 12 years of age (100 mg in 1 teaspoon (tsp) or 5 milliliters (mL).

Weight (lbs)	Weight (kg)	Age (years)	Dose
Under 24	Under 11	Under 2	Consult doctor
24–35	11–16	2–3	1 tsp or 5 mL (100 mg)
36–47	16.3–21.3	4–5	1.5 tsp or 7.5 mL (150 mg)
48–59	21.8–26.8	6–8	2 tsp or 10 mL (200 mg)
60–71	27.2–32.2	9–10	2.5 tsp or 12.5 mL (250 mg)
72–95	32.7–43.2	11–12	3 tsp or 15 mL (300 mg)

Ibuprofen. Dose recommendation for adults and children over 12 years of age is 200 to 400 mg per dose up to four times a day. Children’s ibuprofen has a longer duration of action than acetaminophen and is given every 6 to 8 hours. Table 5.4 has the recommended doses for children aged between 2 and 12 years and table 5.5 for concentrated ibuprofen infants drops.

Products

Aspirin (Bayer Aspirin, Ascriptin, Anacin (contains caffeine as an adjuvant), Bufferin, and Ecotrin (enteric coated aspirin), choline salicylate (Arthropan is a liquid formulation), magnesium salicylate (Mobigesic, Backache Maximum Strength, Extra Strength Doan’s, and Momentum Muscular Backache). NOTE: There is no evidence that any of these products are more effective in treating backache pain than any other aspirin or salicylate product, despite the name of specific products.

Low-dose aspirin (81 mg) products: Bayer Low Dose ‘Baby’ Aspirin, St. Joseph Adult Low Strength Aspirin.

Ibuprofen (Advil, Advil Infants’ Concentrated Drops, Advil Children’s Suspension, Advil Migraine, and Motrin IB, Junior Strength Motrin, Concentrated Motrin Children’s Drops).

Table 5.5 Recommended doses for concentrated ibuprofen infant drops (50 mg in 1.25 mL; special measuring device included in package)

Weight (lbs)	Weight (kg)	Age (months)	Dose
		Under 6	Consult doctor
12–17	5.5–7.7	6–11	1.25 mL (50 mg)
18–23	8.2–10.5	12–23	1.875 mL (75 mg)

Rx-OTC switched NSAIDs

Drug category and indications for use

NSAIDs may be used to reduce fevers and provide temporary relief for minor aches and pains caused by the common cold, sore throat, toothache, headache, muscular aches and pain, backache, premenstrual and menstrual cramps (dysmenorrhea), and pain associated with arthritis.

OTC NSAIDs

Ibuprofen, naproxen sodium and ketoprofen are available as analgesic/antipyretic drugs because manufacturers submitted abbreviated new drug applications. These drugs are available as prescription products but in doses that are higher than those in OTC products. The FDA included ibuprofen in the OTC Internal Analgesic Monograph in 2002.¹⁵

Mode of action

NSAIDs inhibit the synthesis of prostaglandins in peripheral tissues and act in the hypothalamus to reduce a fever in the same manner as aspirin. However, NSAIDs competitively inhibit cyclo-oxygenase in a reversible manner. These NSAIDs cause somewhat less gastric irritation and bleeding than aspirin but require the same warnings.^{5,6}

Warnings and precautions

If individuals are allergic to ibuprofen, naproxen sodium, ketoprofen, or aspirin, or any other analgesic medication, they should not take these products, because they may cause hives, asthma (wheezing), or facial swelling. The drug should be stopped immediately if any of these symptoms occur and a physician contacted.

These products may cause stomach bleeding and the risk of this event is greater if individuals are over 60 years of age, have bleeding problems or peptic ulcer disease, take an anticoagulant drug (blood thinner), take steroids, take any other drugs containing NSAIDs (either OTC or prescription), drink three or more alcoholic beverages a day, take more than the recommended dose, or take the drug for a longer period of time than recommended. A physician or pharmacist should be consulted when taking other drugs if individuals do not know the content of other medications.^{5,6}

If blood appears in any vomiting or the stools have blood or are very black, this may indicate stomach bleeding, and a physician should be consulted immediately. If an individual experiences stomach pain or ringing in the ears, a physician should be consulted.

If the product does not relieve pain within 10 days, or fever within 3 days, a physician should be consulted. If the symptoms worsen or redness develops in the area of the pain, a physician should be consulted. If the product is labeled for sore throat pain, its use should be limited to 2 days.^{1,5}

A physician should be consulted before using these products if the individual has diabetes, high blood pressure, liver cirrhosis, or kidney disease.⁶

These drugs should not be used during the last 3 months of pregnancy unless told to do so by a physician, because they may cause problems for the unborn child and complications during delivery.^{1,5}

Recommended dose

Naproxen sodium. Individuals between the ages of 12 and 65 years of age may take 220 mg (one tablet) every 8 to 12 hours and no more than three tablets within 24 hours. Adults over 60 years of age should take 220 mg (one tablet) every 12 hours. Children under 12 years of age should only take naproxen sodium if recommended by a physician.¹⁶

Ketoprofen. Adults and children over 16 years of age may take 12.5 mg ketoprofen every 8 hours. Children under 16 years of age should only take ketoprofen if recommended by a physician.

Products

Naproxen sodium (Aleve), ketoprofen (marketed as Orudis KT but discontinued by the manufacturer).

Analgesic combinations

The only permitted combination of analgesic drugs is acetaminophen and aspirin.¹

Monograph ingredients

Acetaminophen and aspirin may be combined in a single product. The indications for use of each drug are the same, and the warnings and precautions for each drug must appear on the label. The combination drug may not be labeled for cardiovascular use even though it contains aspirin.

Special warnings for Excedrin Migraine

Individuals should not use Excedrin Migraine for a migraine headache if a physician has never diagnosed their problem as a migraine headache. If this headache is different from previous migraine headaches, is the worst headache of their life, is accompanied by a fever and stiff neck, or has occurred after a head injury, a physician should be consulted. If the headache is caused by bending, coughing or exertion, occurs daily, or is accompanied by vomiting, a physician should be consulted before using this product. Individuals under 18 years of age should not use this product for a migraine headache unless a recommendation has been made by their physician.¹⁶ These warnings are in addition to all other acetaminophen and aspirin warnings that must appear on the label.

Products

Excedrin Extra Strength, Excedrin Migraine, Goody's Headache Powders, Vanquish.

Excedrin Extra Strength and Excedrin Migraine contain exactly the same drugs, acetaminophen (250 mg), aspirin (250 mg) and caffeine (65 mg), but the indications for use and labeled warnings are different. Excedrin Migraine has only one indication, migraine headache, and is labeled for use by individuals over 18 years of age; it has no other intended analgesic or antipyretic use.¹⁷ Both drugs must have a warning for caffeine that states that the recommended dose of this product has caffeine that is about equal to a cup of coffee. Limit intake of caffeine from other sources to avoid nervousness, irritability, increased heart rate, and insomnia that occurs from too much caffeine.¹⁷

Sedatives

Sleep is a dynamic process divided into two components, rapid eye movement (REM) and nonrapid eye movement (NREM), which are easily distinguished by electrophysiological patterns that can be measured using electroencephalography (EEG) and electrooculography (EOG). These patterns vary depending on age of the individual and may be altered by environmental conditions and/or by an individual's mood, emotional state, drug therapy, or disease state.

NREM sleep has four stages, each stage being considered to be a deeper form of sleep. Stage 1 is the transition to sleep phase or the period for onset of sleep. Stage 2 is an intermediate stage, which accounts for approximately 40 to 50% of sleep. Stages 3 and 4 are deep sleep stages where EEG measurements show slow-moving waves. Stages 3 and 4 account for approximately 20% of sleep time and are primarily responsible for the restorative nature of sleep, described by individuals as feeling more alert and energetic after sleep. Stage 4 sleep becomes shorter in duration as people age and is partly responsible for the early awakening experienced by elderly individuals.¹⁸

REM sleep patterns are more complex and less predictable than NREM patterns and are associated with dreams. There is complete relaxation of voluntary muscles during NREM sleep, and memory enforcement occurs during this time. As the amount of REM sleep increases during the night, there is a decrease in stages 3 and 4 of NREM sleep. Individuals usually progress through four or five cycles of sleep (NREM and REM) during the night, with each cycle lasting approximately 90 to 120 minutes.¹⁸

Sleep is not a period where all biological systems shift into a lower activity level for a type of rest up or power up for the next day. Many important activities occur during sleep, for example growth hormone and cortisol (hydrocortisone) are secreted during sleep.

Insomnia is a general term that describes sleep disorders, and the most common complaint by healthy individuals is that of not being able to fall asleep readily, a sleep induction problem. The FDA's definition of an OTC sedative or nighttime sleep-aid is an agent that helps individuals who have

occasional difficulty in falling asleep.¹² However, sleep is affected by external and internal factors, and individuals as well as pharmacists should have an understanding of the sleep process to determine when self-care may be appropriate.

The internal or intrinsic control for sleep is the suprachiasmatic nucleus (SCN) in the hypothalamus of the brain, which increases its neuronal signals as evening approaches (diminishing light), stimulating the pineal gland to secrete the hormone melatonin. Melatonin levels increase until about 2 to 4 a.m. and begin to diminish as dawn approaches. Estrogen and progesterone levels in the brain also affect the SCN and are probably responsible for the fact the women have a higher incidence of insomnia during menstruation and menopause. Postpartum women also have more problems with insomnia.¹⁸

The normal circadian rhythm in humans is slightly more than 24 hours. However, external cues, primarily light and darkness and the daily activities of individuals, entrain the daily rhythm to a 24 hour pattern and keep it at 24 hours. Light, either sunlight or bright artificial light, enters through the eyes, activating neural pathways to the brain to promote wakefulness. Physical activity, social interactions, and a busy or noisy environment also promote wakefulness.

Individuals who experience occasional insomnia should be evaluated for external causes of the problem before drug therapy is initiated. Behaviors that enhance readiness for sleep in individuals include no napping during the day, tapering down physical activity at the end of the day, having a regular pattern of activity to prepare for sleep, having a regular time to go to sleep, reducing distracting environmental factors such as too much light or noise, controlling the temperature so it is not too hot or too cold, avoiding stimulating drugs (caffeine in any form, pseudoephedrine or phenylephrine in allergy or cough/cold medications) in the evening, avoiding alcohol, and avoiding smoking. If these practices do not solve the individual's insomnia, OTC sedative or dietary supplements may help to alleviate the problem.

Common causes of sleep problems include shift work, jet travel, anxiety and stressful situations, and medical conditions such as asthma, chronic obstructive pulmonary disease, depression, sleep apnea, pain, dementia, and rhinitis, among others. Treatment of the medical condition by a physician should be the first attempt at solving sleep problems associated with medical problems.

Shift workers and travelers who going through numerous time zones have difficulties because each of these situations imposes new cues on the body's internal circadian rhythm. Melatonin has some positive effects in these situations, but prescription drugs are usually more effective. If shift work is a long-term employment situation, altering circadian rhythm by entrainment methods using light therapy and behavior modification may be successful.

Individuals who suffer from lack of sleep often complain of tiredness, fatigue, lack of mental alertness, decreased motor skill, lack of concentration, and irritability. Frequently, individuals try to compensate for these effects by using stimulant drugs.

OTC drugs

Monograph drug: diphenhydramine

Drug category and indications for use

Nighttime sleep-aid or sedative relieves occasional sleeplessness for individuals who have difficulty in falling asleep.¹⁹

Mode of action

Antihistamines classified as first generation or sedating antihistamines produce their effect by acting in the CNS.

Warnings and precautions

If diphenhydramine does not provide relief of sleeplessness within 2 weeks, a physician should be consulted because a more serious condition may be the problem. If an individual has asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, or difficulty in urinating because of an enlarged prostate, a physician should be consulted. Alcoholic beverages should not be consumed while taking diphenhydramine. If an individual is taking other sedatives or tranquilizers, a physician should be consulted before using this drug.¹⁹

Recommended dose

Adults and children over 12 years of age may take a single dose of 50 mg of diphenhydramine 30 minutes before bedtime. This product should not be used if any other product containing diphenhydramine is being used, even if it is for topical use.²⁰

NOTE: Diphenhydramine is used in many oral products for allergies, sinus congestion, cough/colds, and itching, as well as topical products for insect bites and itching. There are many reports of toxicity because of the use of several products containing diphenhydramine.²⁰

Products

Diphenhydramine: (Benadryl, Nytol, Simply Sleep, Sominex, Unisom Sleep Gels, and Unisom Sleep Melts).

Rx-OTC switched drug: doxylamine

Doxylamine is an approved antihistamine with sedative actions similar to diphenhydramine that was not included in the FDA's nighttime sleep aid monograph. The manufacturer filed an abbreviated new drug application with the FDA and received approval for its use as a sedative.²¹

Drug category and indications for use

OTC sedatives relieve sleeplessness caused by difficulty in falling asleep.

Mode of action

Antihistamines classified as first generation or sedating antihistamines produce their effect by an action in the CNS.

Warnings and precautions

If doxylamine does not provide relief of sleeplessness within 2 weeks, a physician should be consulted because a more serious condition may be the problem. If an individual has asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, or difficulty in urinating because of an enlarged prostate, a physician should be consulted. Alcoholic beverages should not be drunk while taking doxylamine. If an individual is taking other sedatives or tranquilizers, a physician should be consulted before using this drug.²¹

Recommended dose

Adults and children over 12 years of age may take a single dose of 25 mg doxylamine 30 minutes before bedtime.

Product

Doxylamine (Unisom Sleep Tabs).

Combination sedatives and analgesics

Drug category and indications for use

The FDA has approved the combination of nighttime sedatives with oral analgesics to relieve occasional sleeplessness.

Mode of action

Mild discomfort and pain may prevent individuals from falling asleep easily, and the combination of an analgesic and sedative may be more beneficial than a sedative by itself.

Warnings and precautions

Acetaminophen, aspirin, or ibuprofen may be combined with diphenhydramine. Warnings and precautions for each active ingredient must appear on the label of the product.

Recommended dose

Adults and children over 12 years of age may take a single dose of 1000 mg acetaminophen with 50 mg diphenhydramine hydrochloride 30 minutes before bedtime. Adults and children over 12 years of age may take a single dose of 1000 mg aspirin with 72 mg diphenhydramine citrate 30 minutes

before bedtime. Adults and children over 12 years of age may take a single dose of 400 mg ibuprofen with 72 mg diphenhydramine citrate 30 minutes before bedtime.

Products

Acetaminophen and diphenhydramine (Tylenol PM), aspirin and diphenhydramine (Bayer Aspirin PM), ibuprofen and diphenhydramine (Advil PM).

Dietary supplements

Melatonin

Although melatonin is a human hormone, it is not regulated as an OTC drug by the FDA. It is available from animal sources or from a chemical synthetic process as a dietary supplement. The body synthesizes melatonin through several metabolic steps beginning with the conversion of the amino acid tryptophan to serotonin and ultimately to melatonin.

Numerous studies have been conducted to determine the efficacy of melatonin as a sleep aid. Although many clinical trials reported positive results compared with placebos, the results were not statistically significant in many studies.²² Most of the clinical trials had small numbers of patients and were for short durations of use.

The evidence for the use of melatonin for jet lag in travelers has some positive results for travel in an eastward direction if travel was through three to five time zones, but the requirement for precise timing of dosing melatonin for at least 3 days before the scheduled trip may limit its usefulness.^{22–24} Melatonin when combined with light therapy is more effective in altering an internal circadian rhythm mechanism, but self-care is not appropriate because it involves situations where insomnia is long term, not short term.²⁴

Mode of action

Administration of exogenous melatonin elevates normal circulating levels of melatonin, especially in individuals who have levels less than normal blood concentrations, and it helps to relieve occasional insomnia. It acts at the same receptor sites in the brain as endogenous melatonin.²⁵

Warnings and precautions

Melatonin has no serious adverse effects but may cause fatigue, headache, dizziness, and irritability, especially when higher doses are used (more than 3 mg).

Recommended dose

Adult doses for falling asleep should be 1 to 3 mg 30 to 60 minutes before bedtime. Adult doses for preventing jet lag are 1 to 3 mg taken at the projected time of the new sleep pattern, beginning 3 days before travel.

Products

Melatonin (Melatonex and many generic manufacturers).

Valerian

Valeriana officinalis is the source of extracts that contain valepotriates, sesquiterpenes, and amino acids that are used in dietary supplements promoted as sleep aids. However, the type of preparation used (tablets of valerian extracts, teas or liquid preparation) vary greatly in the quantity of the compounds that are in the product. There are many fewer studies reported on the effectiveness of valerian, but the results, like those for melatonin, show slight benefit for insomnia when compared with placebos.

Mode of action

The exact mechanism by which valerian causes sedation is not known, but it may bind to gamma-aminobutyric acid (GABA) receptors, which normally reduce brain stimulation. It does not exert its full effect unless it is taken for 2 to 4 weeks. This certainly exceeds recommendations for occasional drowsiness, but it should be remembered that dietary supplements are not held to the rigorous standards of OTC drugs because they are not approved for use by the FDA.

Warnings and precautions

Reported adverse effects include GI upset, headache, and morning drowsiness.

Recommended dose

One cup of valerian tea made from a root extract is recommended several times a day. Tablets containing 500 to 1000 mg valerian root extract may be taken 1 hour before bedtime. An alcoholic liquid extract is available and the recommended dose is 15 to 20 drops.²⁶

Product

Valerian (Alluna).

Stimulants

The only OTC drug used as a stimulant is caffeine, but many brewed coffees and teas, or energy drinks, may contain more caffeine than that permitted by the FDA in OTC drugs. Guarana is a plant source of caffeine that appears in many energy or natural products. Table 5.6 lists the amount of caffeine available in some popular beverages and energy drinks.

Drug category and indications for use

Stimulant drugs produce an effect in the CNS that helps to alleviate occasional drowsiness and fatigue and to increase mental alertness.²⁷

Table 5.6 Caffeine content of popular beverages and energy drinks^a

Product	Usual size (ounces)	Caffeine content (mg)
Plain, brewed coffee	8–12	60–120
Plain, brewed, decaf coffee	8–12	< 10
Dunkin' Donuts	16	143
MacDonald's Large	16	145
Starbucks Coffee Grande	16	330
Starbucks Grande Cappuccino	16	150
Starbucks Grande Caffè Latte	16	150
Starbucks Espresso	1.5	77
Plain, brewed tea	8–12	20–90
Lipton Brisk Ice Tea	20	50
Snapple Iced Tea	16	42
Starbucks Tazo Chai Tea	12	75
Nestea Ice Tea	16	34
Coca-Cola	12	35
Diet Coke	12	45
Barq's Root Beer	12	23
Mountain Dew	12	55
Dr. Pepper	12	41
Pepsi	12	38
Full Throttle	16	144
TAB Energy	10.5	95
Jolt	23.5	280
Vault	12	70
So-Be Adrenaline Rush	16	152
So-Be No Fear	16	174
Rockstar	16	160
Red Bull	8.3	80
Propel Invigorating Water	20	50
Vitamin Water Energy	20	40

^aCaffeine in drinks: <http://www.energyfiend.com/the-caffeine-database> (accessed: February 28, 2009).

Caffeine appears in many headache remedies because it increases the pain-relieving effect of OTC analgesics (see earlier discussion in this chapter). Caffeine also produces a mild diuretic effect and is used for this purpose in products that treat symptoms associated with premenstrual tension (Chapter 6).

Monograph drugs

Caffeine is the only approved monograph drug.

Mode of action

Caffeine stimulates the release of neurohormones, norepinephrine and epinephrine, in the brain, which increase mental alertness and ward off feeling of tiredness and fatigue.

Warning and precautions

Ingestion of caffeine from other sources should be limited when using a caffeine product to prevent nervousness, irritability, insomnia, and rapid heart beat. The product contains approximately as much caffeine as a cup of coffee. If drowsiness or fatigue persists, a physician should be consulted.²⁷

Recommend dose

Adults and children over 12 years of age may take 100 to 200 mg of caffeine every 3 to 4 hours.

Products

Caffeine (NoDoz Maximum Strength, Ultra Pep-Back, Vivarin).

Antidepressant dietary supplements

St. John's wort

Diagnosis and treatment of depression is not a self-care problem and the FDA has not approved any OTC drugs for depression. However, individuals who think they are depressed may try taking OTC stimulants or dietary supplements such as St. John's wort. St. John's wort is widely used in Europe as an antidepressant, particularly in Germany. It is a dietary supplement in the USA and its sale does not require FDA approval. It is commonly used to treat mild to moderate depression.

Clinical trials comparing St. John's wort with placebo and low-dose tricyclic antidepressant drugs have demonstrated a positive effect, and it has fewer adverse effects than the tricyclic antidepressants.²⁸

Drug category and indications for use

St. John's wort is a flowering plant or shrub whose extracts are used to promote a positive mood.

Mode of action

Products of St. John's wort are standardized based on the concentration of hypericin present in the product. Hypericin has weak effects by inhibiting the

reuptake of several neurotransmitters in the brain, including serotonin, nor-epinephrine and GABA. The plant also contains flavonoids, which contribute to its effect.^{29,30} St. John's wort affects liver enzymes, especially cytochrome oxidase (CYP3A4).

Warnings and precautions

If individuals are taking other medications physician should be consulted because St. John's wort has many drug interactions. It decreases the effect of many drugs, including protease inhibitors and nonnucleoside reverse transcriptase inhibitors (used to treat HIV infections), oral contraceptives, cyclosporine, simvastatin, and warfarin. A sunscreen should be used when going outdoors because this product causes photosensitivity reactions.^{29,30}

Because this drug is a dietary supplement, it must contain the following statement: 'This product has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.'

Recommended dose

The daily dose for adults is 300 mg three times a day. This product is not recommended for children. It may take up to 2 months for St. John's wort to produce its full effect.³⁰

Case study exercises

Case 1 A 48-year-old woman tells the pharmacist that she uses two tablets of Tylenol Extra Strength (500 mg of acetaminophen per tablet) four times a day because she fell and her back is sore. She wants to know if she should use Tylenol PM to help her sleep better.

The pharmacist advises her not to use Tylenol PM because she is already taking the maximum recommended daily dose of acetaminophen. If she exceeds the recommended daily dose, she increases the risk of damaging her liver. If she is having trouble falling asleep, she could take a nighttime sedative containing diphenhydramine, such as Nytol, Sominex, or Simply Sleep.

Case 2 The mother of an 11-month-old infant asks the pharmacist what dose of Tylenol Infant Drops she should give the baby because the baby is teething and is cranking and crying.

The pharmacist tells the mother that Tylenol Infant Drops should not be administered to a child less than 2 years of age unless the doctor has advised her to do so. She could purchase a topical product such as Anbesol, which contains a local anesthetic, that is rubbed on the gums to relieve teething pain. (See Chapter 7.)

Case 3 A 56-year-old man who is not under the care of a doctor asks the pharmacist what dose of aspirin he should take to reduce the risk that he could have a heart attack. He is overweight like his father, who died from a heart attack.

The pharmacist recommends that he see a physician because using aspirin for a potential cardiovascular problem is not a decision that should be made by an individual. There are risks associated with the use of aspirin that must be evaluated before he should take aspirin on a daily schedule. The pharmacist explains that he should see a physician because he is overweight, and his father's health history may increase the risk he has for cardiovascular disease.

Case 4 A 44-year-old man had minor dental surgery done and the dentist recommended that he take an OTC anti-inflammatory drug such as ibuprofen for the moderate pain that he is having. He asks the pharmacist if there is some other drug that he could take that does not have to be taken every 4 hours because his job is such that he can't take the medication that frequently.

The pharmacist explains that naproxen sodium (Aleve) is the same type of drug as ibuprofen and has a longer duration of action and would solve his problem. It may be used twice a day.

Case 5 The mother of a 9-year-old girl tells the pharmacist that her daughter has a dance performance in a week and she is too excited and nervous to fall asleep. She asks if using valerian tablets (Alluna) would be suitable because it's a natural product.

The pharmacist advises her not to use any nighttime sedative because sedatives should not be used in children under 12 years of age without a doctor's recommendation. He also tells her that valerian would not be helpful because it takes approximately 2 weeks for it to have its optimum effect. He discusses methods to have the child get ready for bed at a set time and to have her avoid excitement and any beverages like cola drinks that contain caffeine in the late afternoon and evenings.

Case 6 A worker has just had a job change and complains of problems falling asleep at night. When he gets up in the morning, he feels tired and has no energy. He wants to know if Vivarin will help to give him energy during the day.

The pharmacist discusses the man's use of coffee and tea during the day. The man usually gets a 16 ounce Starbucks Grande Coffee on his way to work but he doesn't think it helps him with his fatigue. The pharmacist explains that Vivarin contains 200 mg caffeine and the

Starbucks coffee he drinks contains 330 mg caffeine. The pharmacist suggests that he not consume more caffeine since the coffee he drinks doesn't help him.

The pharmacist discusses an alternative of using a nighttime sedative such as diphenhydramine (Nytol, Somnex or Simply Sleep) or doxylamine (Unisom) for several nights. Perhaps he has some anxiety because of his new job and a few nights of a more restful sleep will help him. If this suggestion isn't satisfactory, he should see his doctor.

Case 7 The mother of a 15-year-old girl asks the pharmacist which OTC migraine drug would be best for her daughter.

The pharmacist discovers that the daughter has never seen a doctor about her headaches. The pharmacist tells the mother that OTC migraine products are only intended for use in individuals who are over 18 years of age and who have been diagnosed as having migraine headaches. The pharmacist recommends contacting the doctor and suggests using acetaminophen or ibuprofen as soon as the headache symptoms occur. The dosing directions on the product label should be followed until the appointment with the doctor.

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