CHAPTER 74

Central Nervous System Stimulants

Patricia K Sonsalla, PhD

Assistant Professor of Neurology
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
Piscataway, NJ 08854

Central nervous system (CNS) stimulants are substances which increase excitability within various regions of the brain or spinal cord. The prominent effects produced by many of these drugs are arousal and increased motor function which result in subjective feelings of increased mental alertness, decreased fatigue, improved concentration, increased energy and motivation and an elevation in mood. Excessive excitation can lead to convulsions, and most, if not all, of these drugs produce seizures in a dose-dependent manner.

Excitability of the CNS reflects an intricate balance between excitatory and inhibitory activity within the brain. Stimulants of the CNS directly or indirectly enhance excitatory activity or block inhibitory components. The excitatory transmitters, glutamate and aspartate, are important neurotransmitters at excitatory synapses where their actions are mediated through *N*-methyl-D-aspartate (NMDA) or non-NMDA (kainate or AMPA/quisqualate) receptors. In contrast, gamma-aminobutyric acid (GABA) and glycine are prominent inhibitory neurotransmitters. The neuromodulator, adenosine, also plays an important role in CNS excitation in that it can exert a depressant action, most likely on the basis of its ability to decrease impulse-generated transmitter release and to limit excitation of postsynaptic elements by direct hyperpolarization. Many CNS stimulants produce excitation through their antagonism at GABA, glycine or adenosine receptors whereas others, the indirect-acting sympathomimetics, produce pronounced CNS stimulation by enhancing the actions of endogeneous catecholamines due to their ability to increase release and/or prevent the uptake of endogenous catecholamines (see Table 1).

The CNS stimulants are much less imporant therapeutically than the CNS depressants, but they can produce dramatic pharmacological effects and some frequently are abused. For example, CNS stimulants (eg, methylphenidate) are among the most commonly prescribed drugs for *attention deficit disorders* in children. The amphetamines or their analogs are used in narcolepsy, as adjunct therapy in *attention deficit disorders* and as *appetite suppressants* in *obesity*. The mild CNS stimulants, such as caffeine, are used in drug-induced *respiratory* and/or *circulatory depression* and *vascular headaches;* caffeine also is used in a number of analgesic combinations. The strong CNS stimulants, such as pentylenetetrazol and picrotoxin, have no established therapeutic use since the therapeutic dose is very close to the convulsant dose.

A number of CNS stimulants have therapeutically useful actions on other parts of the body, and a number of drugs not included in this chapter stimulate the CNS when administered in toxic doses. For example, caffeine, a classical central nervous system stimulant, has clinically useful actions on the heart, blood vessels and kidneys. On the other hand, atropine and ephedrine, drugs with primary actions on the peripheral autonomic nervous system, stimulate the CNS.

Only those drugs which have central stimulation as a predominant action are listed in this section. Those agents whose central stimulant properties are secondary (atropine, many sympathomimetic amines, nicotine, lobeline, carbon dioxide, cyanide, apomorphine and emetine) and those whose central stimulant properties are induced only with toxic doses (phenol, salicylates, local anesthetics, ergot alkaloids, etc) are listed in other chapters. For convenience, the drugs described are divided into three groups: xanthine derivatives, psychostimulants and miscellaneous CNS stimulants.

Xanthine Derivatives

Stimulation of the CNS can be produced in man and animals by a large number of natural and synthetic substances. None, however, occupy as prominent a place in the environment of man as do the xanthine derivatives. The most popular sources of these substances are the xanthine beverages, which include coffee, tea, cocoa and cola-flavored drinks. Coffee and tea contain caffeine, whereas cocoa contains theobromine. The caffeine content of tea leaves (2 to 3%) is higher than that of coffee beans (0.7 to 2.0%) but the beverages as finally prepared contain about equal amounts of this stimulant. Caffeine is present in amounts of about 100 to 150 mg/180 mL of brewed coffee; 60 to 80 mg/180 mL of instant coffee; 40 to 100 mg/180 mL of tea and 17 to 55 mg/180 mL of cola beverage. There is little doubt that the popularity of these beverages depends on their stimulant action, although most people are unaware of any stimulation.

Xanthine derivatives include caffeine, theobromine, theophylline and a number of related synthetic derivatives, all of which have similar pharmacological properties that differ markedly in the intensity of their actions in various structures. For example, the stimulant effects of caffeine and theophylline on the CNS and on skeletal muscle are much greater than those of theobromine. Furthermore, theophylline surpasses caffeine in its diuretic, cardiac and smooth muscular actions. Therefore, in the therapeutic application of these drugs for a specific effect, side effects can be minimized and the desired effect intensified by careful selection of the xanthine employed.

The principal therapeutic application of caffeine is as a CNS stimulant. Therefore, caffeine and its congeners which possess this effect will be discussed in this section. The principal therapeutic use of theophylline and related compounds is as a bronchodilator in the management of asthma. For this reason theophylline derivatives are discussed in Chapter 56, *Respiratory Drugs*.

Aminophylline—page 971.

Caffeine

1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-, Theine: Nō Dōz (*Bristol-Myers*); Tirend (*Norcliff Thayer*); Vivarin (*Beecham*); Dexitac (*Republic*); Quick Pep (*Thompson*)

1,3,7-Trimethylxanthine [58-08-2] $C_8H_{10}N_4O_2$ (194.19); *monohydrate* [5743-12-4] (212.21).

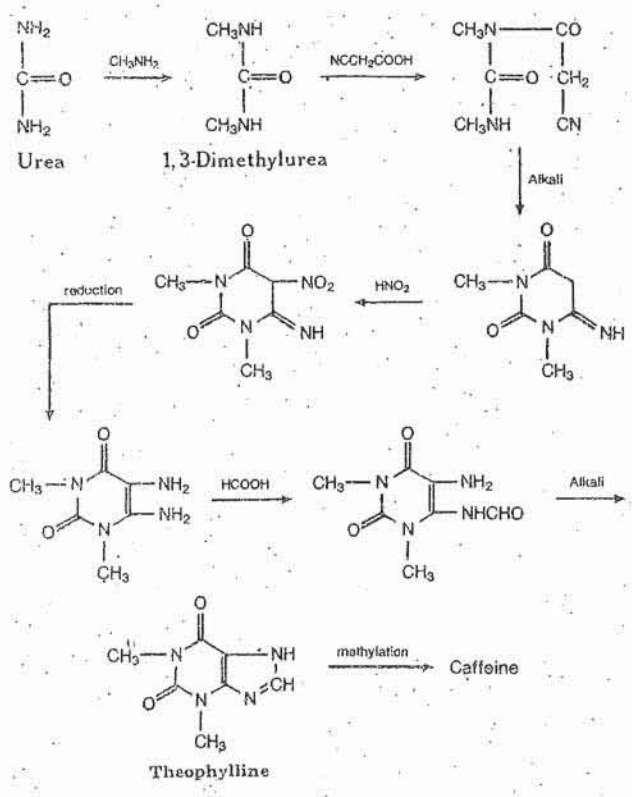
For the structural formula, see page 404.

Preparation—Caffeine may be isolated from tea or coffee by boiling with water in the presence of lime or magnesium oxide, which serves to precipitate the tannins and some of the coloring matter. After filtration, the crude caffeine that separates is recrystallized from hot water after

Table 1—Various Classes of CNS Stimulants and Representative Compounds

Class	Compound	Mechanism
Xanthines	Caffeine	Adenosine antagonist
	Theophylline	Adenosine antagonist
Psychostimulants	Amphetamines	Enhance actions of endogenous catecholamines
	Methylphenidate	
	Cocaine	
	Mazindol	
	Pemoline	
	Diethylpropion	
Miscellaneous stimulants	Bicuculline	Competitive GABA antagonist
	Picrotoxin	Non-competitive GABA antagonist
	Pentylenetetrazol	Non-competitive GABA antagonist
	Strychnine	Competitive antagonist at non-NMDA glycine receptor
	Doxapram	Unknown

treatment with decolorizing charcoal. A source of the commercial supply is tea dust or sweepings. Increasing quantities of caffeine are now obtained as a by-product in the manufacture of "decaffeinized coffee." It is also produced by methylation of theobromine (partial synthesis) and by total synthesis from urea or dimethylurea by variations of Traube's classic process (*Ber 33*: 3052, 1900). The essential steps of a synthesis of theophylline and caffeine from urea are shown below:



Description—White powder or white, glistening needles, usually matted; odorless and has a bitter taste; pH (1% solution) 6.9; the hydrate is efflorescent in air and loses all its moisture at 80°; when rendered anhydrous by drying, melts between 235° and 237.5°; pK_a 13.9.

Solubility—1 g of anhydrous caffeine dissolves in about 50 mL water, 6 mL water at 80°, 75 mL alcohol, about 25 mL alcohol at 60°, about 6 mL chloroform or 600 mL ether. Being a weak base, caffeine does not form stable salts, and even its salts of strong acids, such as the hydrochloride or hydrobromide, are hydrolyzed readily by water. The solubility of caffeine in water is increased by the presence of organic acids or their alkali salts, eg, benzoates, salicylates, cinnamates or citrates and this is the reason for the use of several such preparations.

Uses—Used orally as a mild *CNS stimulant* to aid in staying awake and to restore mental alertness in fatigued patients. In combination with ergotamine tartrate it is used to abort *vascular headaches* such as migraine and cluster headaches. It often is used in combination with analgesics (acetaminophen, aspirin, etc) for the treatment of mild pain. Since its analgesic activity is suspect, such use is controversial. It is used in combination with antihistamines and other sedative agents to overcome the sedative properties of such drugs; however, effective dosage for this purpose has not been established adequately. It is used parenterally in the form of caffeine and sodium benzoate for the treatment of *respiratory depression* associated with overdosage of CNS depressant drugs (narcotic analgesics, alcohol, etc). Because of the questionable benefit of such use and its transient action, most authorities believe caffeine and other analeptics should not be used in these conditions and recommend other supportive therapy. Finally, caffeine is used orally either alone or in combination with other drugs (analgesics, diuretics, etc) to relieve tension and fluid retention associated with menstruation. In view of its minimal diuretic action, its usefulness in this condition is questionable.

Caffeine and citrated caffeine are absorbed well following oral administration. Absorption by the oral route is more rapid than that after intramuscular injection. Absorption from suppositories following rectal administration is slow and erratic. Following the oral administration of 100 mg of caffeine (as in coffee), peak plasma levels of about 1.5 to 1.8 μg/mL are reached after 50 to 75 min. Following oral administration of 250 mg to "caffeine-naive" subjects, peak plasma levels of 4.2 to 26 μg/mL are reached in a mean time of 60 min. Therapeutic plasma concentrations range from 6 to 13 μg/mL; concentrations >20 μg/mL commonly produce adverse reactions. The lethal concentration is >100 μg/mL. It is distributed rapidly throughout all body tissues, readily crossing the placenta and blood-brain barrier. Approximately 17% of the drug is bound to plasma proteins. Plasma half-life is 3 to 4 hours in adults. Plasma half-life in neonates born of women given caffeine prior to delivery has been estimated to be about 80 hr. The drug is metabolized rapidly by the liver to 1-methyluric acid, 1-methylxanthine and 7-methylxanthine. About 10% is excreted unchanged by the kidneys.

For many years it was thought that the stimulant actions of caffeine were due to its inhibition of the enzyme phosphodiesterase in the brain and the resulting accumulation and actions of cyclic 3',5'-adenosine monophosphate (c-AMP). However, several compounds which are more potent than caffeine in inhibiting phosphodiesterase activity lack CNS stimulant actions. Moreover, the concentration of caffeine needed to inhibit phosphodiesterase activity is 100 times greater than blood levels achieved after caffeine consumption. Rather, substantial evidence indicates that the stimulant actions of caffeine are due to its blockade of adenosine receptors. Adenosine exerts prominent presynaptic and postsynaptic inhibition of neuronal activity. Blockade of this inhibition by caffeine likely is responsible for its stimulant effects.

In one double-blind clinical study, oral administration of 250 mg of the drug to nine healthy young non-coffee drinkers who had no coffee, tea or cola in the previous 3 wk *increased plasma renin* activity 57%, plasma *norepinephrine* 75% and plasma *epinephrine* by 207%; urinary *normetanephrine* and *metanephrine* were *increased* 52 and 100%, respectively; mean *blood pressure increased* 14/10 torr within 1 hr; *heart rate* first *decreased* and then *increased*; and *respiratory rate increased* 20%.

Caffeine stimulates all levels of the CNS. In oral doses of 100 to 200 mg, it stimulates the cerebral cortex producing a more rapid and clear flow of thought, wakefulness or arousal in fatigued patients and improved psychomotor coordination. Its cortical effects are milder and of shorter duration than those of the amphetamines. In slightly larger doses, caffeine stimulates medullary vagal, vasomotor and respiratory centers, inducing bradycardia, vasoconstriction and an increased respiratory rate.

The drug exerts multiple effects on the heart. It has a positive inotropic effect on the myocardium and a positive chronotropic effect on the sinoatrial node, causing a transient increase in heart rate, force of contraction, cardiac output and work of the heart. In doses in excess of 250 mg, the centrally mediated vagal effects of caffeine may be masked by increased sinus rates; tachycardia, extrasystoles or other ventricular arrhythmias may result.

Caffeine, in normally ingested amounts, produces vasoconstriction of blood vessels, presumably by blocking adenosine receptors located in the smooth muscle of the vasculature. It is thought that the vasoconstriction of the cerebral blood vessels by caffeine contributes to its ability to relieve headaches. In the peripheral vasculature, caffeine ingestion results in increased vascular resistance and a slight increase in blood pressure, probably due to the action of caffeine on both the smooth muscle of the vessels and on catecholamine release.

Other pharmacological effects of caffeine include the following: it stimulates voluntary skeletal muscle, increasing the force of muscle contraction and decreasing muscular fatigue; it stimulates parietal cells, increasing gastric acid secretion; it induces a mild diuresis by increasing renal blood flow and glomerular filtration rate and decreasing proximal tubular reabsorption of sodium and water; and it stimulates glycogenolysis and lipolysis, but the increases in blood glucose and plasma lipids usually

are not significant in normal patients. Repeated use of this substance may result in the development of tolerance to its diuretic, cardiovascular and central nervous system effects.

This drug and other xanthines may enhance the cardiac inotropic effects of beta-adrenergic stimulating agents and decrease the effect of benzodiazepines. Because caffeine ingestion results in reduced liver blood flow, the metabolism and elimination of drugs which are eliminated primarily by hepatic metabolism may be slowed. The ingestion of caffeine can cause a slight increase in urine levels of vanillylmandelic acid, catecholamines and 5-hydroxyindoleacetic acid. Since high urine levels of vanillylmandelic acid or catecholamines may result in a false-positive diagnosis of pheochromocytoma or neuroblastoma, caffeine intake should be avoided during these tests.

Acute toxicity involving caffeine has been reported only rarely. Overdosage usually is associated with gastrointestinal pain, mild delirium, insomnia, diuresis, dehydration and fever. More serious symptoms include cardiac arrhythmias and convulsions. The acute lethal dose of caffeine in adults appears to be about 5 to 10 g either intravenously or orally. Death has occurred in a child following oral ingestion of 3 g.

Prolonged, high intake may produce tolerance, habituation and psychological dependence. Abrupt discontinuation of the stimulant may result in headache, irritation, nervousness, anxiety and dizziness.

The ingestion of large amounts of combinations containing aspirin and caffeine has been associated with analgesic nephropathy, characterized by sterile pyuria, asymptomatic bacteruria, pyelonephritis, papillary necrosis, interstitial fibrosis and nephritis. The role of caffeine in the etiology of this condition has not been established conclusively. For an indepth review of "The Health Consequences of Caffeine" the interested reader is referred to the interesting article by Sawynok and Yaksh (*Pharmacol Rev* 45: 43, 1992).

Dose—100 to **500 mg**; *usual*, **200 mg** as necessary.

Dosage Forms—Extended-Release Capsules: 200 and 250 mg; Tablets: 100, 150 and 200 mg.

Citrated Caffeine

Caffeine citrate (1:1) [69-22-7]; a mixture of caffeine and citric acid containing 50% $C_8H_{10}N_4O_2$ (anhydrous caffeine) and 50% $C_6H_8O_7$ (anhydrous citric acid).

Preparation—The formula of USP IX was

Caffeine	50 g
Citric Acid	50 g
Distilled Water, hot	100 mL

Dissolve the citric acid in the hot distilled water, add the caffeine, and evaporate the resulting solution to dryness on a water bath, constantly stirring towards the end of the operation. Reduce the product to a fine powder and transfer it to well-closed containers. It is, however, usually prepared by mixing equal proportions of finely powdered anhydrous caffeine and anhydrous citric acid.

Description—White, odorless powder; slightly bitter, acid taste; acid reaction.

Solubility—1 g in about 4 mL warm water, the caffeine gradually precipitating on diluting the solution with an equal volume of water but redissolving on further dilution with sufficient water.

Incompatibilities—Neutralization of the citric acid by *alkalies* or *alkaline salts* will cause precipitation of caffeine if in sufficient concentration. The alkali salts of organic acids may release either caffeine or the free organic acid. In general it displays the incompatibilities of the citric acid which it contains.

Uses—See *Caffeine*.

Dose—100 to **500 mg**; *usual*, **300 mg** as necessary.

Dosage Forms—Tablets: 65 mg.

Caffeine and Sodium Benzoate Injection

A sterile solution of caffeine and sodium benzoate in water for injection; contains an amount of anhydrous caffeine ($C_8H_{10}N_4O_2$) equivalent to 45 to 52%, and an amount of sodium benzoate ($C_7H_5NaO_2$) equivalent to 47.5 to 55.5%, of the labeled amounts of caffeine and sodium benzoate.

Description—pH between 6.5 and 8.5.

Use—See *Caffeine*, page 1231.

Dose—*Parenteral*, **200 mg** to **1 g**; *usual*, **500 mg**, repeated as necessary.

Dosage Form—Injection: 250 mg (Caffeine Anhydrous 125 mg and Sodium Benzoate 125 mg) per mL.

Dyphylline—page 972.

Oxtriphylline—page 972.

Theophylline—page 973.

Theophylline Calcium Salicylate—see RPS-17, page 875.

Theophylline, Ephedrine Hydrochloride and Phenobarbital—page 973.

Theophylline Olamine—see RPS-18, page 868.

Theophylline Sodium Acetate—see RPS-17, page 875.

Theophylline Sodium Glycinate—see RPS-17, page 874.

Psychostimulants

Most of the compounds included under this heading are indirect-acting sympathomimetic drugs and are more potent central stimulants than the xanthine derivatives. These compounds (amphetamine and several of its analogs, cocaine, mazindol, methylphenidate; see Table 1) do not stimulate monoaminergic receptors directly, but rather increase the actions of endogenous catecholamines. This is due to their ability to inhibit the uptake of the catecholamine from the synaptic cleft after release or to cause catecholamine release. Because of their propensity to produce euphoria, many of these drugs are widely abused and are controlled substances. The approved use for most of these drugs is as anorectic agents, although several are used in the treatment of attention deficit disorders (methylphenidate, pemoline, amphetamine) or narcolepsy (amphetamine). Given the abuse liability and dependence potential of many of these compounds, the therapeutic use of these drugs should be monitored closely.

A number of drugs that stimulate the central nervous system are promoted for treatment of hyperactive behavior in children. A degree of hyperactivity which is not acceptable, either at home or at school, often is accompanied by difficulty in learning and sometimes by other neurological signs, such as "clumsiness." Although the usefulness of psychostimulant drugs in treatment of "hyperactivity" has been controversial, there is a patient group with severe, persistent hyperactivity and a short attention span that is likely to benefit from treatment with these agents. The psychostimulants most frequently used for this purpose include *methylphenidate* and *pemoline*.

Amphetamine and methamphetamine are two of the most potent sympathomimetic drugs with regard to CNS stimulation. They can improve psychomotor performance and enhance wakefulness, although it is questionable whether concentration in complex learning situations or judgement is improved. The effects of these amphetamines are thought to be mediated through cortical stimulation and possibly through stimulation of the reticular activating system. The (*S*), or (+), isomer of amphetamine is three to four times more potent than the (*R*), or (−), isomer in elicitation of CNS responses (only the *d* isomer of methamphetamine is available clinically). The alerting effect of the amphetamines, their anorectic effect and some component of their locomotor-stimulating action are likely mediated by norepinephrine release. Some aspects of locomotor activity, as well as euphoria, are due to dopamine release within the basal ganglia and the limbic system.

That the CNS stimulating effects of these compounds are mediated through the catecholamines is suggested by findings in animal studies that inhibition of catecholamine synthesis prevents the behavioral activation produced by the drugs. In humans, acute toxicity produces restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, irritability, weakness, insomnia and fever. Larger doses can produce confusion, increased libido, anxiety, panic states, hallucinations and psychotic behavior. Some of these effects may be due to the release of 5-hydroxytryptamine (5-HT) from serotonergic neurons. In addition, there may be pronounced cardiovascular and gastrointestinal effects. Excessive toxicity results in convulsions, coma and cerebral hemorrhages. See Chapter 57 for more discussion on the amphetamines.

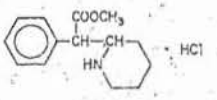
Cocaine is also a potent sympathomimetic CNS stimulant with actions very similar to those of the amphetamines but with a much shorter duration of action. Cocaine has local anesthetic actions; however, its use for this purpose is limited, having been replaced by synthetic local anesthetics which have little CNS stimulation. The importance of cocaine lies

in its abuse potential; it is currently one of the most widely abused drugs in the US. See also Chapters 47 and 68.

Amphetamine Sulfate—page 986.
Benzphetamine Hydrochloride—page 987.
Cocaine—page 1151.
Deanol Acetaminobenzoate—see RPS-18, page 1136.
Dextroamphetamine Phosphate—see RPS-16, page 820.
Dextroamphetamine Sulfate—page 987.
Diethylpropion—page 987.
Mazindol—page 992.
Methamphetamine—page 994.

Methylphenidate Hydrochloride

2-Piperidineacetic acid, (R^*, R^*)-(±)-α-phenyl-, methyl ester, hydrochloride, Ritalin (*Ciba*)



[298-59-9] $C_{14}H_{19}NO_2$,HCl (269.77).

Preparation—2-Chloropyridine is condensed with phenylacetonitrile and the resulting α-phenyl-2-pyridineacetonitrile is hydrated to its corresponding amide. The pyridine ring then is hydrogenated catalytically and the amide converted to its corresponding carboxylic acid. Esterification with methanol, with the aid of HCl, yields the final product.

Description—White, odorless, fine, crystalline powder; melts about 75°; solutions are acid to litmus, pK_a 8.9.

Solubility—Freely soluble in water or methanol; soluble in alcohol; slightly soluble in chloroform or acetone.

Uses—A mild *CNS stimulant* with a potency intermediate to caffeine and amphetamine. Its pharmacological properties are essentially the same as those of the amphetamines. It also shares the abuse potential of the amphetamines. It is *effective* as adjunctive therapy to other remedial measures (psychological, educational and social) in the management of *attention deficit disorders*. Double blind studies with placebo control demonstrate that methylphenidate can improve behavior, concentration and learning ability in 70 to 80% of children with this disorder. Drug treatment is not indicated for all children with this disorder; stimulants are not intended in the child who exhibits symptoms secondary to environmental factors or primary psychiatric disorders. Consequently, these should be ruled out and available psychological, educational and social resources should be used before drug therapy is instituted. It also is *effective* in *narcolepsy* and *possibly effective* in *mild depression*, as well as *apathetic* or *withdrawn senile behavior*.

It appears to be absorbed well from the gastrointestinal tract. Peak blood levels are reached in 1 to 3 hr and the plasma half-life ranges from 1 to 3 hr. The pharmacological effects persist from 4 to 6 hr. Approximately 80% of an oral dose is metabolized to ritalinic acid and excreted in the urine. The mechanism of action has not been determined. It is thought to act on the cerebral cortex and subcortical structures, including the thalamus; stimulation by this drug causes an increase in motor activity, mental alertness, diminished sense of fatigue, brighter spirits and mild euphoria. It also produces an anorexigenic effect.

The drug is contraindicated in patients with anxiety, tension and agitation or those known to be sensitive to the drug. The safe use in children under 6 yr of age has not been established. It also is contraindicated in patients with a prior history of epilepsy or those with EEG abnormalities in absence of seizures and in patients with glaucoma, motor tics or with a family history or diagnosis of *Tourette's syndrome*. It may decrease the hypotensive effect of guanethidine. It should be used with caution in patients on pressor agents or MAO inhibitors. Human pharmacological studies indicate the drug may inhibit metabolism of coumarin anticoagulants, anticonvulsants and tricyclic antidepressants. Dosage of these agents may require downward adjustment when given concomitantly with this drug.

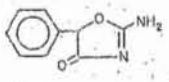
Adverse reactions include nervousness, insomnia, hypersensitivity reactions (including various skin manifestations), anorexia, nausea, dizziness, palpitations, headache, dyskinesia, blood pressure and pulse changes, tachycardia, angina, cardiac arrhythmias, abdominal pain and weight loss. Toxic psychoses, leukopenia, anemia and a few cases of scalp hair loss have been reported. Tolerance, psychic dependence and abnormal behavior have been reported in patients who have abused this drug. Consequently, it should be administered cautiously, if at all, in emotionally unstable patients, those with a history of drug dependency and those known to alter drug dosage on their own initiative.

Dose—*Oral*, **10** to **60 mg** a day; *usual*, **10 mg** 2 or 3 times a day. Sustained-release tablets have an 8-hr duration of action; these may be used when the dose of slow-release (SR) tablets correspond to the 8-hr dose of the drug. Symptoms of overdose may include vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis and dryness of the mucous membranes.

Dosage Forms—Tablets: 5, 10 and 20 mg. Sustained-Release Tablets: 20 mg.

Pemoline

4(5*H*)-Oxazolone, 2-amino-5-phenyl-, Cylert (*Abbott*)



[2152-34-3] $C_9H_8N_2O_2$ (176.17).

Preparation—Ethyl mandelate $C_6H_5CH(OH)COOC_2H_5$, is reacted with guanidine, $HN{=}C(NH_2)_2$, in boiling alcohol solution, US Pat 2,892,753.

Description—White, crystalline powder; odorless and tasteless; melts at about 256° with decomposition.

Solubility—Practically insoluble in water, chloroform, dilute HCl or ether; slightly soluble in alcohol or propylene glycol.

Uses—A *CNS stimulant* which is structurally dissimilar to the amphetamines and methylphenidate. Although laboratory studies indicate that pemoline may act through dopaminergic mechanisms, the mechanism and site of action in man are not known. Indicated as adjunctive therapy in children with *attention deficit disorder*. It also has been used in the treatment of fatigue, mental depression, chronic schizophrenia and as a mild stimulant in geriatric patients; however, clinical benefits from such use are minimal. It should *not* be used for the prevention or treatment of normal fatigue. Peak serum levels of the drug are reached 2 to 4 hr after ingestion of a single oral dose; the serum half-life is approximately 12 hr, and a steady state level is reached in 2 to 3 days of multiple dosage. About 50% of the drug is bound to serum proteins. Approximately 75% of an oral dose is excreted in the urine within 24 hr, about 43% unchanged and 22% as pemoline conjugates.

Insomnia, usually transient, is the principal adverse effect. Anorexia with weight loss may occur during early weeks of therapy; weight gain usually resumes within 3 to 6 mo. Stomachache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness and hallucinations have been reported. Other adverse effects reported include seizures; dyskinetic movements of the tongue, lips, face and extremities; abnormal aculogyric function (nystagmus and oculogyric crises) and symptoms of *Tourette's syndrome*.

It is contraindicated in patients with hypersensitivity or idiosyncrasy to the drug. It is not recommended for children less than 6 yr of age since safety and efficacy in this age group have not been established. Sufficient data on safety and efficacy of long-term use in children are not yet available. Safety for use during pregnancy and lactation has not been established.

Dose—*Oral, initial*, 37.5 mg given as a single dose each morning; may be increased by **18.75 mg** a day at weekly intervals until the desired clinical response is obtained. The effective dose for most patients is **56.25** to **75 mg** a day; the maximum recommended dose is **112.5 mg** a day. Significant benefit from the drug may not be evident until the 3rd or 4th wk of treatment.

Dosage Forms—Tablets: 18.75, 37.5 and 75 mg. Chewable Tablets: 37.5 mg.

Phendimetrazine Tartrate—page 995.
Phenmetrazine Hydrochloride—page 996.
Phentermine—page 996.

Miscellaneous Central Nervous System Stimulants

Included in this category are strychnine and compounds which formerly were referred to as analeptic drugs. The analeptics are substances which stimulate various regions of the brain. Excessive doses may cause the stimulation to spread to motor areas and precipitate convulsions. Analeptics formerly were used in an attempt to counteract severe intoxication by general depressants. However, none of the

compounds is a safe and selective respiratory stimulant, although doxapram is still available for use in certain circumstances. Moreover, depressant drug intoxications can be managed effectively with more conservative measures that stress intensive supportive care. Hence, the airway is kept clear by suction or by endotracheal tube, the patient is turned regularly and oxygen is administered as needed. Shock is overcome by the use of blood or plasma expanders and vasopressors. Where available, dialysis is used to remove the drug.

Although most of the formerly classified analeptics are not used therapeutically nor are available clinically, several have become important research tools for evaluating the efficacy and mechanism of action of various drugs, particularly of anticonvulsants, because the mechanism by which these convulsants exert their actions is well characterized. It is known that strychnine is a glycine antagonist with actions primarily in the spinal cord, whereas bicuculline, picrotoxin and pentylenetetrazol are GABA antagonists which act within various regions of the brain. Strychnine is used as a pesticide for destroying rodents and other predatory animals and thus is encountered frequently as a cause of poisoning in man.

Doxapram Hydrochloride—page 979.

Nikethamide—see RPS18, page 1134.

Pentylenetetrazol—see RPS-18, page 1134.

Picrotoxin—see RPS-18, page 1135.

Pipradrol Hydrochloride—see RPS-15, page 1034.

Racephedrine Hydrochloride—see RPS-17, page 893.

Strychnine—see RPS-18, page 1136.

Theobromine—see RPS-18, page 941.

Theobromine Salts—see RPS-15, page 1070.

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