STIMULANTS

1. Introduction

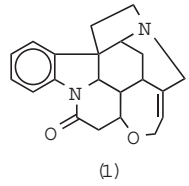
A variety of chemical agents have the capacity to stimulate the central nervous system (CNS) of mammals. Some have therapeutic uses; others are primarily of toxicological importance. The capacity of some of the agents to produce excessive CNS stimulation has greatly limited the usefulness of many in this class of compounds. Excessive CNS stimulation can lead to the production of convulsions, which may have fatal consequences. Herein stimulants are separated into three more or less distinct pharmacological categories: analeptics, psychomotor stimulants, and antidepressants. The therapeutic uses of CNS stimulants continue to increase as a result of the widespread use of newer antidepressants and the increased recognition of the benefits of therapeutic treatment of Attention Deficit Hyperactivity Disorder (ADHD).

2. Analeptics

Analeptics are respiratory stimulants capable of stimulating respiratory and vasomotor centers in the medulla. These have been used to revive individuals poisoned by central nervous depressants, such as barbiturates, alcohol, and general anesthetics. The action is not confined only to the medulla; at doses only slightly higher than those that stimulate the medulla, analeptics can stimulate the motor cortex and produce seizures. The initial CNS stimulation is followed, if larger doses are given, by CNS depression and ultimately by respiratory depression and cardiovascular collapse. Nowadays, analeptics are seldom used to treat overdose by CNS depressants. Controlled studies (1) have shown that a higher incidence of mortality occurred when analeptics were administered to poisoned patients than when the drugs were not administered and the patients received only good nursing care.

Although the clinical usefulness is limited, analeptics continue to be valuable tools in the study of CNS neurotransmitters. A discussion of central neurotransmission is available in a number of textbooks in pharmacology and neuroscience (eg, 2), and elsewhere in this *Encyclopedia*. A large number of chemical substances function in the mammalian CNS to regulate the transmission of information from one neuron to another. Neurotransmitters may be either excitatory or inhibitory (ie, may cause a depolarization or a hyperpolarization, respectively, of the neuronal membrane with which they interact). As a simplification, compounds that antagonize the actions of inhibitory transmitters tend to cause excitation and thus cause convulsions; compounds that facilitate inhibitory neurotransmission tend to be depressants. Conversely, agents that antagonize excitatory neurotransmission tend to be depressants and compounds that facilitate excitatory transmission tend to be convulsants.

Some naturally occurring analeptics have been known for centuries. Two of the best known and most thoroughly studied are strychnine [57-24-9] (**1**) and picrotoxin [124-87-8], a 1:1 combination of picrotoxinin [17617-45-7] (**2**) and picrotin [21416-53-5] (**3**). These continue to be of interest in the study of mammalian neurotransmission.



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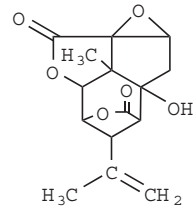

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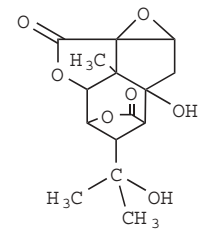

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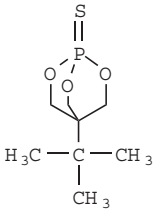
Strychnine (**1**), an alkaloid, was introduced into European medical practice in the early sixteenth century after being used as a rat poison. Strychnine still has some uses as a rodenticide, although its use is more and more restricted. In many countries, its administration is restricted to below ground use to control pocket gophers while it is totally banned in other countries. The total synthesis of this complex molecule is known (3,4).

There is good evidence that strychnine is a specific, competitive, postsynaptic antagonist of glycine in the CNS. Glycine, a known inhibitory transmitter in the mammalian CNS, is primarily located and functions at interneurons in the spinal cord. Glycine mediates inhibition of spinal cord neurons and is intimately involved in the regulation of spinal cord and brainstem reflexes. By directly antagonizing the inhibitory action of glycine, strychnine allows excitatory impulses to be greatly exaggerated, resulting in a characteristic seizure pattern known as opisthotonos. In humans, in whom the extensor muscles are normally dominant, a tonic hyperextension is observed, so that at its extreme, opisthotonos presents as a characteristic posture in which the back is arched and only the back of the head and the heels are touching the surface on which the patient is lying. In the presence of strychnine, all sensory stimuli produce exaggerated responses, and even slight sensory stimulation may precipitate convulsions. An important aspect of therapy is therefore to prevent the patient from receiving sensory stimulation.

Picrotoxin has been instrumental in establishing an inhibitory neurotransmitter role for the amino acid, γ-aminobutyric acid (GABA), quantitatively the most important inhibitory neurotransmitter in the mammalian CNS. Whereas glycine is predominately localized in the spinal cord, GABA is more highly concentrated in the brain.

Picrotoxin, unlike strychnine and most other analeptics, is nonnitrogenous. The bitter principle is extracted from the seeds of the Asian shrub, *anamirta panicuilata* or *A. Cocculus* (so-called fishseed plant). Only picrotoxinin (**2**) has analeptic properties. Both picrotoxin and picrotin (**3**) have been synthesized by a multistep process starting with (−)-carvone (5); structures and absolute configurations have also been established (6). On GABAergic neurons in the CNS, there is a GABA binding site, as well as a picrotoxin binding site, among other sites, surrounding the chloride channel (7). GABA acts to promote the influx of chloride into the cell by opening the chloride channel. When picrotoxinin is present, it binds to the picrotoxin-binding site noncompetitively and acts to close the chloride channel, thereby antagonizing the ability of GABA to allow chloride to enter the cell and produce hyperpolarization. Other compounds that appear to

function in a manner similar to picrotoxinin include some bicyclic cage compounds such as (^{35}S)*t*-butylbicyclophosphorothionate (TBPS) (**4**), the convulsant barbiturate isomer *S*(+)*N*-methyl-5-phenyl-5-propylbarbituric acid (*S*(+)MPPB) (**5**), and lindane [58-89-9] (**6**) (8). Pentylenetetrazol [54-95-5] (**7**), one of the first totally synthetic analeptics, is prepared by the reaction of cyclohexanone and hydrazoic acid (9). Pentylenetetrazol, first introduced in the United States in 1927 as a treatment for barbiturate poisoning, was used to a limited extent for chemical shock therapy. It is still used occasionally to enhance mental and physical activity in elderly patients and as a diagnostic aid, ie, as an electroencephalogram (EEG) activator, in epilepsy. Pentylenetetrazol is also an important laboratory tool for evaluating potential anticonvulsant drugs.



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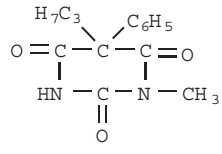

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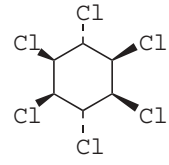

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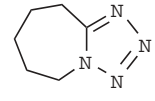

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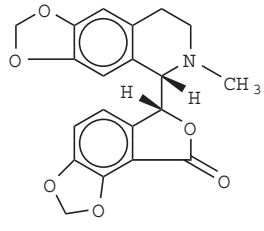

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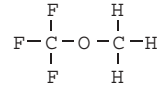

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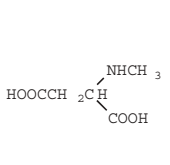
Bicuculline [485-49-4] (**8**) is another analeptic compound known to act by competitively antagonizing GABA at its receptor (9). There is no evidence that bicuculline has been evaluated in humans. Several other compounds, such as the steroid R5135 (10) or the arylaminopyridazines SR 95103 (11) and SR 95531 (12), appear to antagonize GABA competitively in a manner similar to that of bicuculline.

Flurothyl [333-36-8] (bis-(2,2,2-trifluoroethyl)ether) (**9**), an analeptic having strong convulsant properties, has been used for chemical shock therapy (13). The compound is unique in that it is a volatile fluorinated ether and its structure resembles those of many halogenated general anesthetics. Chemical shock therapy is rarely used.

Compounds that have agonistic properties at glutamate or aspartate receptors are also CNS stimulants, readily cause convulsions, and presumably could also be employed as analeptics. Three separate excitatory amino acid receptor subtypes have been characterized pharmacologically, based on the relative potency of synthetic agonists. These three receptors are named for their respec-

tive prototypical agonists: *N*-methyl-D-aspartate [6384-92-5] (NMDA) (**10**), kainate from kainic acid [487-79-6] (**11**), and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) (**12**). All of the agonists, ie, NMDA, kainic acid, and AMPA, are stimulants and convulsants (14). These agents are used only experimentally, but synthetic derivatives of some have been tested clinically.



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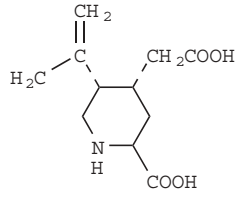

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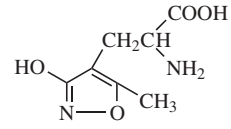
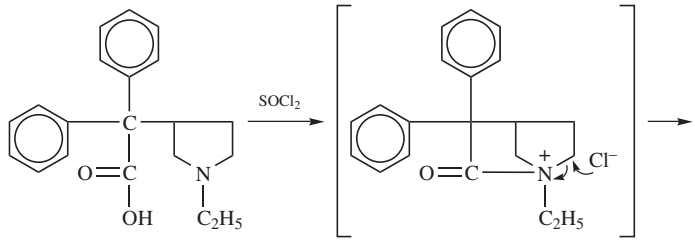
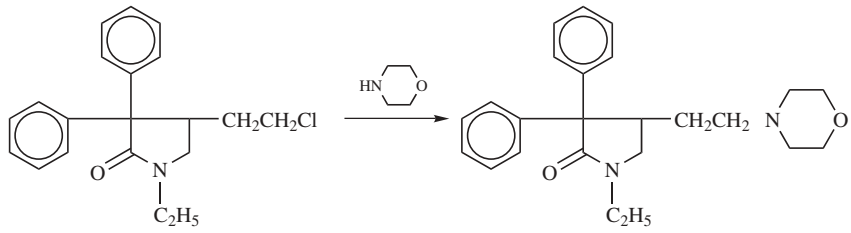


(**12**)

Benzodiazepines have largely replaced barbiturates and barbiturate-like agents for use as anxiolytics and sedative–hypnotics. Because benzodiazepines rarely produce levels of CNS depression that require therapeutic intervention and because of the availability of a compound, flumazenil (Romazicon), that selectively blocks the CNS depressant effects of benzodiazepines (15), the need for analeptics has decreased considerably. However, there are occasions in which the use of a respiratory stimulant may be warranted. By far the leading respiratory stimulant marketed in the United States is doxapram [309-29-5] (**13**), prepared by a unique rearrangement of the pyrrolidine [3471-97-4] (**14**) to the pyrrolidinone [3192-64-1] (**15**), followed by alkylation using morpholine (16).



(**14**)



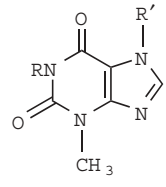
(**15**) (**13**)

2.1. Health and Safety Factors. Clinical side effects of most commercially available analeptics have been summarized (2). Overdoses produce symp-

toms of extreme CNS excitation, including restlessness, hyperexcitability, skeletal muscle hyperactivity, and in some cases convulsions.

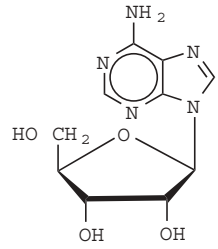
3. Psychostimulants

Compounds having relatively specific cerebral stimulant properties are classified as psychostimulants or psychoanaleptics. Caffeine [58-08-2] (**16**), a mild psychostimulant, has been called the most widely used psychoactive substance on earth (17). Caffeine, theophylline [58-55-9] (**17**), and theobromine [83-67-0] (**18**) are three closely related alkaloids known as methylxanthines that occur in plants widely distributed throughout the world. The first two have CNS stimulant properties; the last is virtually inactive as a stimulant. The basis for the popularity of caffeine-containing beverages is their ability to elevate mood, decrease fatigue, and increase capacity for work. It is estimated that at least half the population of the world consumes tea on a regular basis; in the United States, coffee is the most important source of caffeine, and cola-flavored drinks seem a close second. The word caffeine is used exclusively herein even though some of the effects of caffeinated beverages may result from the theophylline content. The effects of low to moderate amounts of caffeine ingestion are generally salutary. At higher levels, however, more serious signs of CNS stimulation may be elicited. These may be expressed as nervousness, restlessness, insomnia, tremors, and anxiety. At even higher doses, generalized convulsions may occur.



(16, R = R′ = CH_3)
(17, R = CH_3; R′ = H
(18, R = H; R′ = CH_3)

The mechanism by which the methylxanthines produce CNS stimulation is not clearly established. These agents may function, in part, to limit chloride channel activation in a manner similar to that of pentylenetetrazol (**7**) or bicuculline (**8**). Another possibility is a specific antagonism of the inhibitory neurotransmitter adenosine [58-61-7] (**19**) (18).



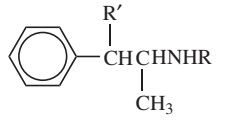
(19)

Methylxanthines have a few valid therapeutic uses, including treatment of asthma and relief of dyspnea. The CNS stimulatory effects are also utilized for the treatment of the prolonged apnea that may be observed in premature infants. Caffeine citrate may be the agent of choice for the treatment of apnea of prematurity (AOP) although theophylline is probably the most widely used (19). Doxapram may be used, if a switch to a different class of agents is desired. For parenteral administration, a salt of theophylline is employed. There are several salts available, including theophylline ethylenediamine (aminophylline [317-34-0]) and oxtriphylline (choline theophyllinate). Other synthetic xanthines that are used include dyphylline [479-18-5] and enprofylline [41078-02-8] (20). Caffeine is obtained in pure form from tea waste, from the manufacture of decaffeinated coffee, and by total synthesis (21,22).

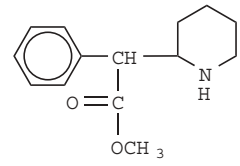
3.1. Sympathomimetics. Sympathomimetics are a group of mostly synthetic compounds that resemble the neurotransmitters epinephrine [51-43-4] and norepinephrine [51-41-2] pharmacologically and to some extent chemically. These agents have wide-ranging pharmacological effects, including, in some cases, profound CNS excitatory actions. Sympathomimetics that have selective central effects have been used in the treatment of narcolepsy, as an aid in weight reduction, and in the treatment of ADHD. The mechanism of action of the sympathomimetics in exerting their central effects is thought to be either directly, by interacting with an adrenoceptor (usually α-1-adrenoceptor) as an agonist, or indirectly, by causing the release of endogenous norepinephrine, which activates all adrenoceptors. Only a limited number of agents having sympathomimetic activity demonstrate CNS properties, ie, those that are able to penetrate the blood–brain barrier by virtue of their lipid solubility.

The oldest of the centrally acting sympathomimetics is ephedrine [299-42-3] (**20**), used for over 5000 years in China before being introduced into Western medicine in 1924 (23). Ephedrine occurs in many varieties of plants of the genus, Ephedra, and may also be synthesized. Although formerly used extensively for its CNS effects as well as for its bronchodilator properties, more effective and more selective agents have largely replaced ephedrine. There are three other indirectly acting adrenomimetic compounds having CNS stimulant properties that have been employed clinically: amphetamine [300-62-9](**21**) , methamphetamine [537-46-2] (**22**), and methylphenidate [113-45-1] (**23**). d-Amphetamine is three to four times more potent in producing CNS stimulation than is L-amphetamine. Dextroamphetamine has been used to overcome fatigue, as an analeptic, as an aid in weight reduction, and in the treatment of ADHD. As of this writing,

amphetamine is used to some extent in the therapy of narcolepsy, but is seldom used for weight reduction, even though it has marked effect on decreasing appetite (anorexic effect). Because tolerance develops rapidly to the anorexic effects, the weight loss is of limited duration ($\sim$ 2–3 weeks). The development of tolerance, the abuse potential, and the insomnia and nervousness it causes have led to a marked reduction in amphetamine usage. Indeed, legal restrictions have markedly curtailed the production, as well as the availability, of both (**21**) and (**22**). Methylphenidate (**23**) is reported to have less abuse potential and appears to be the drug of choice for ADHD (24).

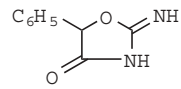


(**20,** R = CH_3; R′ = OH)
(**21,** R = R′ = H)
(**22,** R = CH_3; R′ = H)



(23)

Pemoline [2152-34-3] (**24**), structurally dissimilar to amphetamine or methylphenidate, appears to share their CNS-stimulating properties. Consequently, pemoline also is employed in the treatment of ADHD and of narcolepsy. There are several other compounds that are structurally related to amphetamines, although not as potent and, presumably, without as much abuse potential. These compounds also have anorexic effects and are sometimes used to treat obesity. Two related compounds that have been used to treat obesity are phentermine [122-09-8] and fenfluramine [458-24-2]. This combination, known as Phen-fen, was taken off the market when it was discovered to cause a high incidence of abnormal heart valve pathology. Phentermine remains on the market for short-term treatment of obesity. An agent that is available over-the-counter, phenylpropanolamine [1483815-4], is used occasionally (25). A related compound with little CNS stimulatory activity, pseudoephedrine, has been employed in the illicit manufacturing of methamphetamine. It formerly was available over the counter, but the Combat Methamphetamine Epidemic Act of 2005 caused its use to be markedly restricted. All preparations (antihistamihnics or decongestants) containing pseudoephedrine are required to be dispensed by pharmacists and usage records are maintained at the pharmacy.



(24)

Side Effects and Abuse Potential. Sympathomimetics are one of the most abused classes of drugs marketed in the United States. Continued use for weight loss and relief of fatigue leads to the development of tolerance and habituation. There is widespread use of amphetamine, as well as other sympathomimetic compounds, among recreational drug users. The abuse characteristics of

amphetamines and related drugs are similar to that of cocaine [50-36-2], also a sympathomimetic. Acute intoxication from amphetamine-like drugs results in the patient exhibiting dizziness, confusion, tremor, irritability, hypertension, and cardiac palpitations. Acute paranoia and a state resembling schizophrenia may also be exhibited by individuals taking large amounts of amphetamines or cocaine (26). Because of the potential for abuse, the manufacture, distribution, and use of sympathomimetics are strictly controlled in the United States by the Drug Enforcement Agency (DEA).

3.2. Other Drugs for Treatment of Attention Deficit Hyperactivity Disorder. Although sympathomimetics remain the drugs of choice for this disorder, other agents are also used. Atomoxetine is the first nonstimulant that has been approved for the treatment of ADHD (24).

For many years, it appeared that ADHD was becoming an epidemic in the United States and other countries, but the medication for this disorder has leveled off in recent years, indicating that the incidence of ADHD is not significantly increasing (24).

4. Antidepressants

4.1. Depression. Disorders of mood or affect may be either a pathological state or a normal human emotion. The American Psychiatric Association has established diagnostic criteria that allow clinicians to distinguish between patients who require treatment and those who do not. It is estimated that $\sim$ 5% of the adult population of the United States may be suffering from a mood disorder at any one time (27). The most common mood disorder, known as reactive depression, is commonly observed following adverse life events, such as the death of a loved one. It may also be an accompaniment to other serious physical illnesses, such as heart attacks, cancer, or debilitating diseases, such as Parkinson's disease and alcoholism. In addition, depression may be an adverse effect of drugs, such as certain antihypertensives. Reactive depression is frequently expressed by depression, anxiety, or feelings of stress or guilt. Patients usually recover spontaneously, but medication and counseling frequently speed up the process. In contrast to reactive depression, the two principal mood disorders, unipolar disorder and bipolar disorder, appear to be genetically determined biochemical disorders that are lifelong diseases. Frequent swings between serious depression and reasonably normal behavior often result. These behavioral swings can make evaluation of therapeutic effectiveness extremely difficult (28).

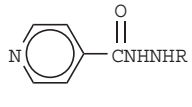
The most common type of depression, known as unipolar disorder (major depression), accounts for $\sim$ 25% of all depression. Signs include weight loss, loss of libido, alterations in sleep pattern, symptoms of negative self-image, suicidal thoughts, and overwhelming grief. The other type is known as bipolar disorder (manic–depressive disorder), and includes $\sim$ 10–15% of depressions. Typically, the patient having bipolar disorder alternates between depression as seen in unipolar depression, and periods in which the symptoms are exactly the opposite: seemingly boundless energy, excessive talkativeness, increased libido, inflated self-esteem, and surges of creativity. The patient having bipolar illness cycles between depression and mania, in which the duration of each cycle is

commonly measured in months. The patient having unipolar disorder, on the other hand, is usually in a state of constant depression (28).

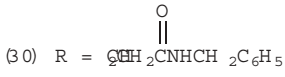
4.2. Mechanism. The mechanisms involved in the etiology of mood disorders have been derived from an understanding of the mechanism of action of the drugs that are effective in the therapy of the disorders. The monoamine oxidase inhibitors were the first effective drugs for the treatment of depression. Their mechanism of action is to elevate levels of those endogenous agents, eg, monoamines such as norepinephrine, dopamine [51-61-6], and serotonin [50-67-9], that are substrates for the enzyme monoamine oxidase (MAO). Compounds that decrease the concentrations of these same monoamines, such as reserpine [50-55-5], cause many of the signs and symptoms of depression. Many studies monitoring regulation of various monoamine receptors in the CNS have led to two important experimental findings. One is a down-regulation of β-adrenoceptors following chronic administration of many drugs effective in depression. The other is an enhancement of transmission through a particular receptor, 5-HT_{1A}, after chronic administration of all clinically effective antidepressants and after electroconvulsive treatment. A detailed review of the neuropharmacology of antidepressants is available (28).

4.3. Treatment. Most, although not all, of the drugs effective in the treatment of depression are CNS stimulants. Until the middle of the twentieth century, pharmacological treatment was symptomatic, supportive, and frequently ineffective. Patients having suicidal tendencies, a common finding in depression, were isolated for their own protection. The development around the 1900s of psychotherapy and the discovery in the 1930s of the use of chemoshock, utilizing pentylenetetrazol or insulin treatment, and electroconvulsive therapy (ECT) gave the first indication that depression could be successfully treated. The discovery in the 1950s of agents known as monoamine oxidase inhibitors (MAOI) and later of the tricyclic antidepressants (TCA) has led to more effective and safer preparations.

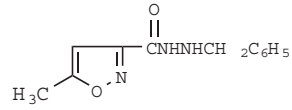
4.4. Monoamine Oxidase Inhibitors. The MAOIs inactivate the enzyme MAO, which is responsible for the oxidative deamination of a variety of endogenous and exogenous substances. Among the endogenous substances are the neurotransmitters, norepinephrine, dopamine, and serotonin. The prototype MAOI is iproniazid [54-92-2] (**25**), originally tested as an antitubercular drug and a close chemical relative of the effective antitubercular, isoniazid [54-85-3] (**26**). Only three agents are currently available: isocarboxazid [59-63-2] (**27**), phenelzine [51-71-8] (**28**), and tranylcypromine [155-09-9] (**29**).



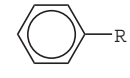
(25, R = $CH(CH_3)_2$)
(26, R = H)



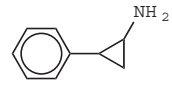
(30) R = $CH_2CH_2CNHCH_2C_6H_5$



(27)



(28, R = $CH_2CH_2NHNH_2$)
(31, R = $CH(CH_3)NHNH_2$)



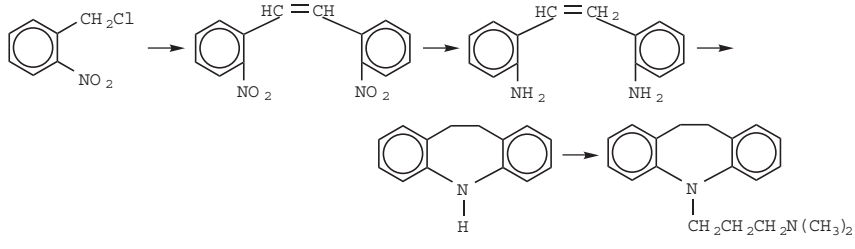
(29)

Nialamide [51-12-7] (**30**) and mebanazine [65-64-5] (**31**) are two MAO inhibitors marketed in Europe that have structural similarities to iproniazid and phenelzine, respectively. Both compounds are prepared by standard methods.

The use of MAOIs for the treatment of depression is severely restricted because of potential side effects, the most serious of which is hypertensive crisis, which results primarily from the presence of dietary tyramine. Tyramine, a naturally occurring amine present in cheese, beer, wine, and other foods, is an indirectly acting sympathomimetic, ie, it potently causes the release of norepinephrine from sympathetic neurons. The norepinephrine that is released interacts with adrenoceptors and, by interacting with α-adrenoceptors, causes a marked increase in blood pressure; the resultant hypertension may be so severe as to cause death.

Normally, dietary tyramine is broken down in the gastrointestinal tract by MAO and is not absorbed. In the presence of MAOI, however, all of its potent sympathomimetic actions are seen. Other side effects of MAOI include excessive CNS stimulation, orthostatic hypotension, weight gain, and in rare cases hepatotoxicity. Because the monoamine oxidase inhibitors exhibit greater toxicity, yet no greater therapeutic response than other, newer agents, clinical use has been markedly curtailed. The primary use for MAOIs is in the treatment of atypical depressions, eg, those associated with increased appetite, phobic anxiety, hypersomnolence, and fatigues, but not melancholia (28).

4.5. Tricyclic Antidepressants. Imipramine [50-49-7] (**32**), which was the first tricyclic antidepressant to be developed, is one of many useful psychoactive compounds derived from systematic molecular modifications of the antihistamine promethazine [60-87-7]. The sulfur atom of promethazine was replaced with an ethylene bridge and the dimethylamino group attached to an *n*-propyl group, rather than to an isopropyl one, of the side chain. The actual synthesis of (**32**) is typical of the compounds in this class (28).



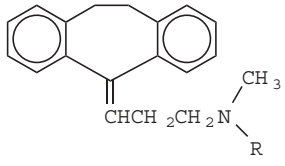
(32)

Early studies on its mechanism of action showed that imipramine potentiates the effects of the catecholamines, primarily norepinephrine. This finding, along with other evidence, led to the hypothesis that the compound exerts its antidepressant effects by elevating norepinephrine levels at central adrenergic

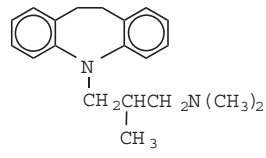
synapses. Subsequent studies have shown that the compound is a potent inhibitor of norepinephrine reuptake and, to a lesser extent, the uptake of serotonin, thus fitting the hypothesis that had been developed to explain the antidepressant actions of MAOIs.

Following the successful introduction of imipramine (**32**), many related compounds were prepared and clinically evaluated for antidepressant effects. Amitriptyline [50-48-6] (**33**), structurally related to imipramine but having a C=CH group replacing the heterocyclic $N-CH_2$ fragment, has comparable pharmacological and clinical effects to imipramine. Both are particularly useful in the treatment of depressed patients exhibiting psychomotor agitation. Trimipramine [739-71-9] (**34**), which is also structurally similar to imipramine, differing only in the branched side chain, has similar activity as the latter, but is slightly less potent.

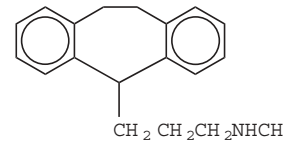
Desipramine [50-47-5] (**35**) and nortriptyline [72-69-5] (**36**) are demethylated derivatives and principal metabolites of (**32**) and (**33**), respectively. Both compounds possess less sedative and stronger psychomotor effects than the tertiary amine counterparts, probably because tricyclics containing secondary amine groups generally show greater selectivity for inhibiting the reuptake of norepinephrine compared with the reuptake of serotonin. Protriptyline [438-60-8] (**37**), a structural isomer of nortriptyline, is another important secondary amine that displays a similar clinical profile.



(33, R=CH_3)
(36, R=H)

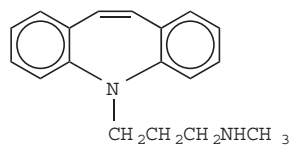


(34)

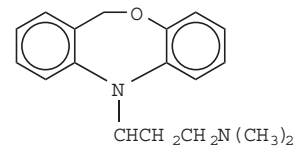


(35)

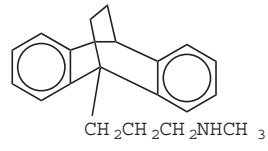
Doxepin [1668-19-5] (**38**), unlike other commercially available tricyclics, has an oxygen atom in the bridge between the two aromatic rings. It is marketed as a cis–trans mixture (1:5) of isomers, both of which are active. This close relative of amitriptyline (**33**) has both sedative and anxiolytic properties associated with its antidepressant profile. Maprotiline [10262-69-8] (**39**) and amoxapine [14028-44-5] (**40**) are pharmacologically, although not chemically, similar to the tricyclic secondary amines. Clomipramine [303-49-1] (**41**) has similar pharmacological and antidepressant efficacy. However, clomipramine is approved by the U.S. Food and Drug Administration (FDA) only for the treatment of obsessive–compulsive disorder.



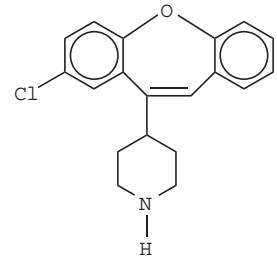
(37)



(38)



(39)



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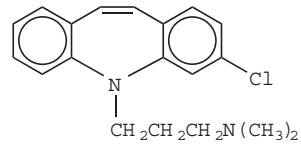
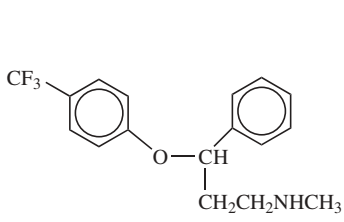


(41)

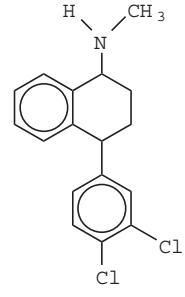
Side Effects and Toxicity. Adverse effects to the tricyclic antidepressants, primarily the result of the actions of these compounds on either the autonomic, cardiovascular, or central nervous systems, are summarized in Table 1. The most serious side effects of the tricyclics concern the cardiovascular system. Arrhythmias, which are dose-dependent and rarely occur at therapeutic plasma levels, can be life-threatening. In order to prevent adverse effects, as well as to be certain that the patient has taken enough drug to be effective, the steady-state serum levels of tricyclic antidepressant drugs are monitored as a matter of good practice. A comprehensive review of structure–activity relationships among the tricyclic antidepressants is available (29).

4.6. Selective Serotonin Reuptake Inhibitors. In 1987, the FDA approved fluoxetine [54910-89-3] (**42**) for use in the treatment of major depression. Fluoxetine and related compounds, sertraline [79617-96-2] (**43**), and paroxetine [61869-08-7] (**44**) appear to inhibit selectively the reuptake of serotonin while having virtually no effect on the uptake of norepinephrine or dopamine. It is hypothesized that the elevated levels of serotonin that occur at the synapse as the result of decreased uptake in time produces a desensitization of certain serotonin receptors, eg, 5-HT_{1A} and 5-HT_{1B} (30). Ultimately, these events are believed to lead to a potentiation of serotonin neurotransmission at central synaptic sites. In addition to its effects on serotonin, sertraline has been shown to produce a down-regulation of β-adrenoceptors following chronic admin-

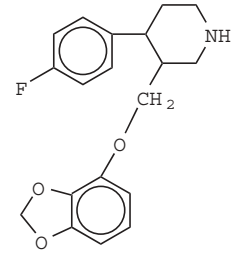
istration. These selective serotonin reuptake inhibitors (SSRIs) do not appear to be more effective than the tricyclics for the treatment of depression. However, the SSRIs do appear to lack many of the side effects associated with the tricyclics and other antidepressants, and are therefore both safer for and more readily accepted by the patient. Sexual dysfunction is a common complaint of most antidepressants. The principal side effects of the SSRIs appear to consist of headache, nausea, and restlessness. A summary of adverse effects of the SSRI drugs available in the United States is provided in Table 2.



(**42**)

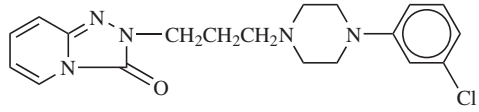


(**43**)

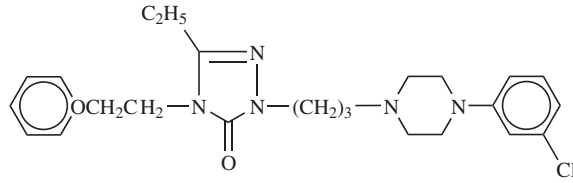


(**44**)

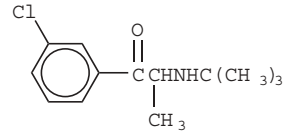
4.7. Miscellaneous Antidepressants. There are a few agents that either chemically or pharmacologically do not fit neatly into any of the categorized antidepressant agents. Trazodone [19794-93-5] (**45**) was introduced as a safer, less toxic, and faster-acting antidepressant. It is effective in some patients, virtually ineffective in others. Trazodone, which appears to have effects at both serotonin and norepinephrine synapses, causes a high level of sedation, as well as dizziness, hypotension, and nausea. It is also reported to cause priapism, an uncommon, but serious side effect. Nefazodone (**45a**) is similar in structure to trazodone and appears to share most of its clinical and pharmacological effects. Although priapism did not occur during early clinical studies, this is still a possibility considering the structural similarities with trazodone. Buprion [34911-55-2] (**47**) is devoid of inhibitory actions on both serotonin and norepinephrine uptake systems. However, it is a potent inhibitor of the uptake system for dopamine. Buprion is also not a monoamine oxidase inhibitor. It is well tolerated by patients of all ages, including the elderly, and is virtually devoid of cardiovascular and antimuscarinic side effects, particularly when compared with the tricyclics. However, buprion is a CNS stimulant and can cause convulsions at higher doses. More commonly, nervousness and insomnia are observed. These drugs are included in Table 1.



(**45**)



(**45a**)

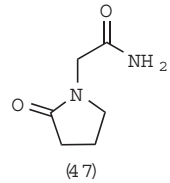


(46)

4.8. Other Drugs. Agents not considered to be CNS stimulants yet employed for the treatment of certain types of depression includes lithium carbonate for the treatment of bipolar disorder. In many patients, lithium is the sole agent used to control manic behavior and is very effective. However, some compounds approved initially as antiepileptic agents, also have been approved for bipolar disorder. These are of different structures and include valproic acid, lamotrigine, and clonazepam. Olanzapine, a benzodiazepine, is also approved to treat bipolar disorder.

There are other chemical substances with slight CNS properties that have been suggested as being potentially useful for a variety of conditions. Nootropics is a term that has been used to describe drugs that might be useful in increasing cognitive function. The obvious utility of such agents would be in the treatment of dementias, particularly Alzeheimer's disease. The first drugs that were approved by the FDA for Alzheimer's disease are inhibitors of acetylcholine (cholinesterase inhibitors). They are relatively well tolerated, but their effectiveness is minimal.

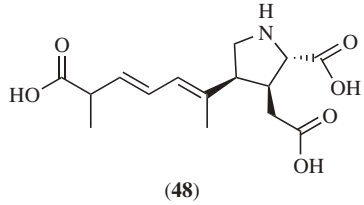
Many other agents, particularly nutritional supplements have been claimed to be useful in the treatment or prevention of dementia, but none have been approved for this use by the FDA. One agent worth mentioning is piracetam [7491-74-9] (**47**). It is available in parts of Europe and has been tested for effectiveness in a variety of situations, including post-stroke aphasia, epilepsy, dementia, among other conditions. Unfortunately, no well-controlled clinical studies have been reported.



(47)

There are two compounds with stimulant properties that have been isolated from red algae. These compounds, domoic acid (**48**) and kainic acid (**11**), are neu-

rotoxins and can cause short-term memory loss, brain damage, and even death. These two agents are thought to have caused neurological damage in marine mammals. They are thought to act by stimulating AMPA (glutamate) receptors (31).



(**48**)

The market for antidepressant medication is very large. The market in the United States is $\sim\$6 \times 10^9$/year.

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Table 1. **Clinical Features of Antidepressants**[a]

Agent or class	CNS effects[c]	Cardiovascular effects[b]		Anticholinergic effects[b]	Weight change
		Orthostatic hypotension	Arrhythmias		
MAOI	+	+++		++	+
TCA	−	+++	++	++++	+
SSRI[d]	+	0	0	+	−
buprion	+	0	0	+	0
trazadone	−	++	0	+	+

[a]Ref. 29.
[b]No effect, 0; increasing effect, +, ++, +++, and ++++.
[c]Stimulation, +; sedation, −.
[d]Selective serotonin reuptake inhibitor = SSRI.

Table 2. **Selective Serotonin Reuptake Inhibitors**[a]

Generic (trade) name	Common features of all	Specific features
Fluoxetine (*Prozac*)	inhibit neuronal uptake of serotonin(5-HT); cause increased risk of suicide in children and adolescents with major depressive disorder (MDD) and other conditions; cause upper GI bleeding; contraindicated to use with MAOI; require several days to demonstrate efficacy	more insomnia; long half-life; may cause weight loss
Sertraline (*Zoloft*)		more insomnia; more GI side effects; less CNS stimulation
Paroxetine (*Paxil*)		less insomnia; more weight gain
Citalopram (*Celexa*)		less drug–drug interactions
Escitalopram (*Lexapro*)		s-enantiomer of citalopram; less insomnia; less drug–drug interactions

[a]Ref. 29.