Kirk-Othmer Encyclopedia of Chemical Technology.

PSYCHOPHARMACOLOGICAL AGENTS

Until the early 1950s only rudimentary pharmacotherapy was available for the treatment of significant psychiatric illnesses. As of the middle 1990s, agents effective in treating prevalent psychiatric disorders, such as mood disorders, schizophrenia, anxiety disorders, insomnia, and substance use disorders, as well as dementias of diverse etiologies, are available. Nevertheless, improved drugs to treat such central nervous system (CNS) disorders continue to represent one of the greatest medical needs in modern medicine (see Neuroregulators). The therapy of cognitive disorders, particularly age-related dementia which has intensified in the face of the demographic trend toward an increasingly aged population, is only one area receiving increased medical attention (see Antiaging agents; Memory-enhancing drugs). During the latter part of the twentieth century, significant advances were made in the diagnosis and classification of psychiatric illnesses. This has resulted in a much finer differentiation of disorders based on both epidemiological data and clinical response to available psychopharmacological agents as evidenced by the improved classification systems provided in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (1) and the *International Statistical Classification of Diseases and Related Health Problems* (2).

Among the most important psychopharmacological agents initially added to the medical armamentarium were the benzodiazepines, for treating anxiety, insomnia, and for inducing sedation (see Hypnotics, sedatives, anticonvulsants, and anxiolytics); the phenothiazines and thioxanthenes, for treating schizophrenia; as well as diverse tricyclics and hydrazide derivatives for treating depression. Continued emphasis has been placed on achieving further increases in symptomatic efficacy but, additionally, weight is given to improving the side-effect profile. Together these trends have resulted in a more favorable therapeutic index for many of the newer psychopharmacological agents. Indeed, effective and safe pharmacotherapy is available for many psychiatric disorders. Future advances are expected to focus increasingly on achieving the optimal therapy for the subcategories of disorders, some of which have no approved pharmacotherapy available.

Despite recognized successes of psychopharmacology, significant challenges remain. The causative factors underlying most neuropsychiatric disorders are, as of 1996, only poorly understood. Missing is the discovery of psychopharmacological agents which directly impact on the etiological or pathophysiological processes underlying psychiatric illnesses. There is considerable structural diversity among the compounds approved for therapeutic use for each of the principal psychiatric disorders. Focus herein is placed on the most important prescription drugs marketed worldwide for treatment of psychiatric illnesses.

1. Anxiolytics, Sedatives, and Hypnotics

Anxiety disorders and insomnia represent relatively common medical problems within the general population. These problems typically recur over a person's lifetime (3, 4). Epidemiological studies in the United States indicate that the lifetime prevalence for significant anxiety disorders is about 15%. Anxiety disorders are serious medical problems affecting not only quality of life, but additionally may indirectly result in considerable

morbidity owing to association with depression, cardiovascular disease, suicidal behavior, and substance-related disorders.

Insomnia is a related psychiatric illness having potentially serious consequences. In any given year up to one-third of the general population may experience insomnia and consequently considerable impact on quality of life. Potentially serious psychosocial, health, and socioeconomic consequences may follow. Many sedative–hypnotics additionally have a firmly established position within the field of anesthesiology as premedication, inducing agents, and/or for maintenance in intensive care medicine.

1.1. Classification of Anxiety Disorders and Insomnia

Anxiety is an emotional state dominated by the perception or anticipation of danger to physical and/or psychic integrity, well-being, and self-esteem or simply the fear of being unable to adequately cope with problems of daily life. In general, anxiety disorders are more prevalent in women than men. Normally anxiety plays an important adaptive role. When irrational and excessive, however, anxiety is maladaptive and can seriously interfere with daily functioning. According to the DSM-IV classification system (1), anxiety disorders are categorized as the following: (*1*) panic disorder, involving discrete periods of intense fear or discomfort with or without agoraphobia; (*2*) agoraphobia, involving the fear of open, public places or being in a crowd, without a history of panic disorder; (*3*) specific phobia, involving marked, persistent, and excessive fear in the presence or in anticipation of a specific object or situation; (*4*) social phobia, involving severe and persistent fear of humiliating oneself in a social or performance situation; (*5*) obsessive–compulsive disorder, involving recurrent and persistent intrusion of unwanted thoughts, impulses, or images (obsessions) often accompanied by repetitive behaviors (compulsions) performed in order to reduce anxiety and distress; (*6*) post-traumatic stress disorder, resulting from experience of intense fear, helplessness, or horror in connection with events that involved actual or threatened serious injury leading to persistent reexperiencing of the traumatic event; (*7*) acute stress disorder, involving detachment and derealization following exposure to a traumatic event; and (*8*) generalized anxiety disorder, involving recurring excessive anxiety and worry for at least six months which is difficult to control.

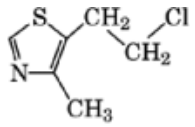
In view of the prominent role played by anxiety as a symptom in all of these disorders, it has been hypothesized that they may, in fact, share a common etiology. Stress and overreaction to stress appears to be involved in the pathophysiology of anxiety. Anxiety disorders often include such clinical features as motor tension, autonomic hyperactivity, hypervigilance, and apprehension. Both physiological and pathological anxiety can be life-threatening when occurring in the face of preexisting organic disorders and may create or perpetuate various physiological dysfunctions.

Insomnia complaints are common in the general population and can be dichotomized into problems of delayed sleep onset and those related to sleep maintenance. Increasing attention is being focused on the adverse daytime effects of insomnia. Sleep disturbances become more common with increased age and are more prevalent in women. Sleep complaints arise from very diverse etiologies which prominently include concomitant primary psychiatric disorders, substance-related disorders, and environmental factors. These must be adequately taken into account when making the decision to symptomatically treat the sleep disorder.

1.2. Pharmacological Profiles of Anxiolytics and Sedative–Hypnotics

Historically, chemotherapy of anxiety and sleep disorders relied on a wide variety of natural products such as opiates, alcohol, cannabis, and kawa pyrones. Use of various bromides and chloral derivatives in these medical indications enjoyed considerable popularity early in the twentieth century. Upon the discovery of barbiturates, numerous synthetic compounds rapidly became available for the treatment of anxiety and insomnia. As of this writing barbiturates are in use primarily as injectable general anesthetics (qv) and as antiepileptics. These agents have been largely replaced as treatment for anxiety and sleep disorders.

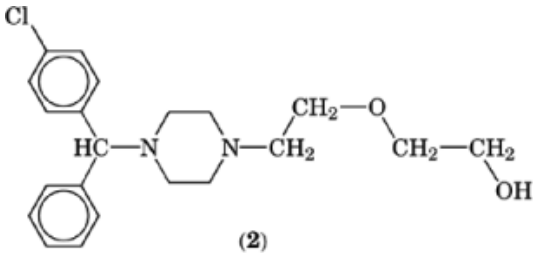
In the 1950s, meprobamate, a propandiole, and methaqualone, a quinazoline, achieved limited clinical importance. Piperidindiones including glutethimide and methyprylon were also used.



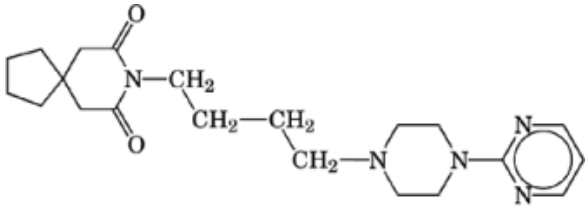
(1)

The short-acting clomethiazole [533-45-9] **(1)**, sometimes used as therapy for sleep disorders in older patients, shares with barbiturates a risk of overdose and dependence. Antihistamines, such as hydroxyzine [68-88-2] **(2)**, are also sometimes used as mild sedatives (see Histamines and histamine antagonists). Antidepressants and antipsychotics which have sedative effects are used to treat insomnia when the sleep disorder is a symptom of some underlying psychiatric disorder.

Beginning in the 1960s, benzodiazepine anxiolytics and hypnotics rapidly became the standard prescription drug treatment. In the 1980s, buspirone [36505-84-7] **(3)**, which acts as a partial agonist at the serotonin [50-67-9] (5-hydroxytryptamine, 5-HT) type 1A receptor, was approved as treatment for generalized anxiety. More recently, selective serotonin reuptake inhibitors (SSRIs) have been approved for therapy of panic disorder and obsessive–compulsive behavior.



(2)



(3)

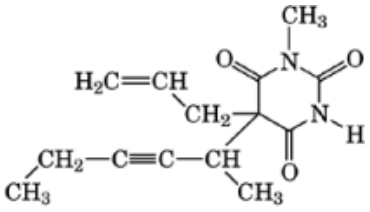
On the basis of available published clinical results, β-adrenergic blockers, particularly propranolol [525-66-6], have sometimes been used off-label to treat anxiety, especially in those patients in which cardiovascular symptoms predominate (5) (see Cardiovascular agents). Clinical results also suggest the possible value of the monoamine–oxidase inhibitor phenelzine [51-71-8] in ameliorating panic disorder with agoraphobia (6). As of the middle 1990s, benzodiazepines continue to dominate the therapy of certain anxiety disorders, eg, generalized anxiety disorder and panic disorder, as well as insomnia.

Barbiturates and benzodiazepines have been demonstrated to act by modulating neurotransmission within the γ-aminobutyric acid [55-12-2] (GABA) system, which is the primary inhibitory neurotransmitter system within the central nervous system. In addition, barbiturates act presynaptically to decrease calcium

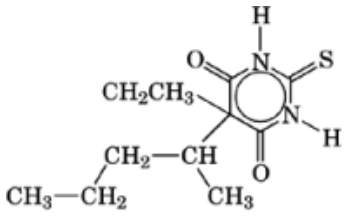
entry, as well as nonsynaptically to decrease voltage-dependent sodium and potassium conductances. The weak sedative effect of the antihistamine hydroxyzine **(2)** is most likely attributable to its antagonism at the histamine-1 receptor. The mechanism of action of meprobamate does not appear to involve the enhancement of GABAergic transmission, whereas methaqualone may do so. Little is known about the mechanism of action of glutethimide and methyprylon.

1.2.1. Barbiturates

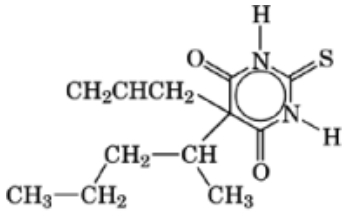
Barbiturates, which by common practice include both oxybarbiturates and thiobarbiturates, are effective as sedative–hypnotics and as anticonvulsants. The clinical effects are the result of allosteric modulation of sites on the $GABA_A$ receptor complex. This increases not only the apparent potency of GABA, but also the maximum effect of GABA. The effects of barbiturates involve the direct alteration of the chloride channel, in contrast to the modulatory effect of benzodiazepines, within the $GABA_A$ receptor complex. Barbiturates enhance GABAergic transmission and at high doses even mimic the effect of GABA itself on chloride conductance by acting via receptors at the post-synaptic membrane, thereby modifying the coupling process between $GABA_A$ receptors and chloride channels or altering the kinetics of the chloride channel. Barbiturates are still occasionally used as alternatives to benzodiazepines in the therapy of anxiety and sleep disorders despite the much narrower therapeutic index of the former drugs and higher liability for abuse and dependence. Barbiturates interact with ethyl alcohol [64-17-5] and other central nervous system depressants.



(4)



(5)



(6)

Barbiturates marketed as psychopharmacological agents are listed in Table 1. The ultrashort-acting barbiturates such as sodium salts of methohexital **(4)**, thiopental **(5)**, and thiamylal **(6)**, are typically used as

intravenous anesthetics, often in combination with inhalation agents. The short- to intermediateacting barbiturates such as secobarbital **(7)**, pentobarbital **(8)**, amobarbital **(9)**, allobarbital **(10)**, and aprobarbital **(11)** are prescribed as hypnotics. The long-acting barbiturates phenobarbital **(12)**, metharbital **(13)**, and methylphenobarbital **(14)** are most commonly used as antiepileptics. Barbiturates, for example butalbital **(15)**, are often components in combination preparations together with paracetamol [103-90-2] (acetaminophen), acetylsalicylic acid [50-78-2] (aspirin), caffeine [58-08-2], and/or codeine [6059-47-8]; sometimes only combination preparations are available. Among the most common adverse effects of barbiturates are ataxia, confusion, drowsiness, hangover, skin rash, and nausea. Many adverse effects of high doses of barbiturates are exaggerations of direct actions observed at therapeutic doses.

Table 1. Marketed Barbiturates

Agentu	Nomen-clature[a]	BAN	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
allobarbital	INN, USAN		[52-43-7]	Diadol	$C_{10}H_{12}N_2O_3$	7
amobarbital	INN, JAN, USAN	amylo-barbitone	[57-43-2]	Amytal (sodium)	$C_{11}H_{18}N_2O_3$	8
amobarbitalsodium	JAN, USAN		[64-43-7]		$C_{11}H_{17}N_2$-NaO_3	8
aprobarbital	INN		[77-02-1]	Alurate	$C_{10}H_{14}N_2O_3$	9
barbital	INN, JAN	barbitone	[57-44-3]	Veronal (sodium)	$C_8H_{12}N_2O_3$	10
barbital sodium	INN	barbitone sodium	[144-02-5]		$C_8H_{11}N_2$-NaO_3	10
benzo-barbital	INN		[744-80-9]	Benzonal	$C_{19}H_{16}N_2O_4$	11
brallo-barbital	INN		[561-86-4]	Vesperone	$C_{10}H_{11}BrN_2O_3$	12
butalbital	INN, USAN		[77-26-9]	Sandoptal	$C_{11}H_{16}N_2O_3$	13
butallylonal sodium			[3486-86-0]	Tempidorm	$C_{11}H_{14}BrN_2$-NaO_3	14
buthalital sodium	INN		[510-90-7]	Baytinal	$C_{11}H_{15}N_2$-NaO_2S	15
butobarbital		butobar-bitone	[77-28-1]	Neonal, Soneryl	$C_{10}H_{16}N_2O_3$	16
carbubarb	INN		[960-05-4]	Nogexan	$C_{11}H_{17}N_3O_5$	
crotarbital			[1952-67-6]	Kalypnon	$C_{10}H_{14}N_2O_3$	17
cyclobarbital	INN	cyclobar-bitone	[52-31-3]	Cyclodorm, Phanodorm	$C_{12}H_{16}N_2O_3$	18
cyclopento-barbital sodium			[302-34-1]	Cyclopal	$C_{12}H_{13}N_2$-NaO_3	11
eterobarb	INN, USAN	eterobarb	[27511-99-5]	Antilon	$C_{16}H_{20}N_2O_5$	19
febarbamate	INN		[13246-02-1]	Solium, Tymium	$C_{20}H_{27}N_3O_6$	11
heptabarb	INN	heptabar-bitone	[509-86-4]	Medomin	$C_{13}H_{18}N_2O_3$	20
heptobarbital			[76-94-8]	Rutonal(e)	$C_{11}H_{10}N_2O_3$	
hexethal sodium			[144-00-3]	Ortal (sodium)	$C_{12}H_{19}N_2$-NaO_3	21
hexobarbital	INN, JAN	hexobar-bitone	[56-29-1]	Evipal (sodium)	$C_{12}H_{16}N_2O_3$	22
metharbital	INN, JAN, USAN	methar-bitone	[50-11-3]	Gemonil	$C_9H_{14}N_2O_3$	23
methitural	INN		[467-43-6]	Neraval, Thiogenal	$C_{12}H_{20}N_2$-O_2S_2	24
methohexital	INN, USAN	methohexi-tone	[151-83-7]	Brevital (sodium)	$C_{14}H_{18}N_2O_3$	25
methohexital sodium	USAN		[309-36-4]		$C_{14}H_{17}N_2NaO_3$	25
methylpheno-barbital[c]	INN	methylpheno-barbitone	[115-38-8]	Mebaral, Prominal	$C_{13}H_{14}N_2O_3$	26
narcobarbital sodium			[3329-16-6]	Eunaron, Narcotal	$C_{11}H_{14}BrN_2$-NaO_3	27
nealbarbital	INN	nealbarbi-tone	[561-83-1]	Cenobal, Nevental	$C_{12}H_{18}N_2O_3$	28
pentobarbital	INN, USAN	pentobarbi-tone	[76-74-4]		$C_{11}H_{18}N_2O_3$	
pentobarbital calcium	JAN		[24876-35-5]		$C_{22}H_{34}CaN_4O_6$	29

Table 1. ***Continued***

Agentu	Nomen-clature[a]	BAN	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
pentobarbital sodium	USAN		[57-33-0]	Nembutal (sodium)	$C_{11}H_{17}N_2NaO_3$	29
phenallymal			[115-43-5]	Alphenate, Sanudorm	$C_{13}H_{12}N_2O_3$	30
phenobarbital	INN, JAN, USAN	phenobarbi-tone	[50-06-6]		$C_{12}H_{12}N_2O_3$	31
phenobarbital sodium	INN, JAN, USAN		[57-30-7]	Luminal (sodium)	$C_{12}H_{11}N_2NaO_3$	31
phetharbital	INN		[357-67-5]	Fedibaretta, Pyrictal	$C_{14}H_{16}N_2O_3$	
probarbital sodium	INN		[143-82-8]	Ipral (sodium)	$C_9H_{13}N_2NaO_3$	32
propallylonal			[545-93-7]	Noctal	$C_{10}H_{13}BrN_2O_3$	33
propylbarbital	INN		[2217-08-5]	Propal, Propanal	$C_{10}H_{16}N_2O_3$	
proxibarbal	INN		[2537-29-3]	Axeen, Ipronal Barbased, Butisol	$C_{10}H_{14}N_2O_4$	34
secbutabar-bital sodium[d]	INN		[143-81-7]	Sodium	$C_{10}H_{15}N_2NaO_3$	35
secbutabar-bital[e]		secbutobar-bitone	[125-40-6]		$C_{10}H_{16}N_2O_3$	
secobarbital	INN, USAN		[76-73-3]	Seconal (sodium)	$C_{12}H_{18}N_2O_3$	36
secobarbital sodium	JAN, USAN	quinalbar-bitone sodium	[309-43-3]		$C_{12}H_{17}N_2NaO_3$	
talbutal	INN, USAN		[115-44-6]	Lutawin	$C_{11}H_{16}N_2O_3$	37
tetrabarbital	INN		[76-23-3]	Butysal, Butysedal Intranarcon,	$C_{12}H_{20}N_2O_3$	
thialbarbital	INN	thialbarbitone	[467-36-7]	Thialpen-ton	$C_{13}H_{16}N_2O_2S$	11
thialbarbital sodium			[3546-29-0]		$C_{13}H_{15}N_2$-NaO_2S	
thiamylal sodium	JAN, USAN		[337-47-3]	Surital	$C_{12}H_{17}N_2$-NaO_2S	38
thiobutabar-bital sodium			[947-08-0]	Brevinarcon	$C_{10}H_{15}N_2$-NaO_2S	39
thiopental sodium	INN, JAN, USAN	thiopentone sodium	[71-73-8]	Pentothal (sodium)	$C_{11}H_{17}N_2$-NaO_2S	40
vinbarbital	INN	vinbarbitone	[125-42-8]	Devinal (sodium)	$C_{11}H_{16}N_2O_3$	41
vinylbital	INN	vinylbitone	[2430-49-1]	Bykonox, Speda	$C_{11}H_{16}N_2O_3$	42

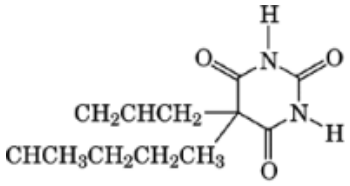
[a]International nonproprietary name (INN), Japanese accepted name (JAN), United States adopted name (USAN), and British approved name (BAN).

[b]Only selected salts are included. Trade names shown can represent the base or any of the salts included in "Nomenclature".

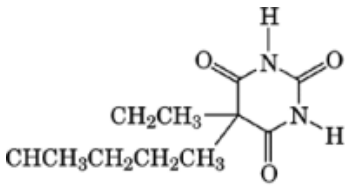
[c]USAN and JAN = mephobarbital.

[d]USAN = butabarbital sodium.

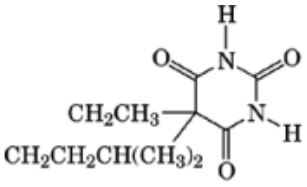
[e]USAN = butabarbital.



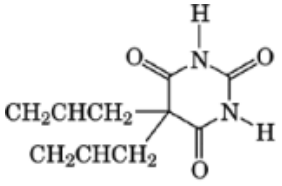
(7)



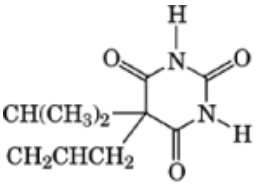
(**8**)



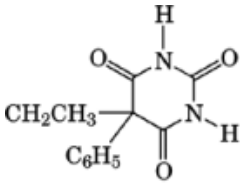
(**9**)



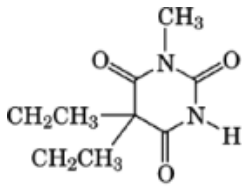
(**10**)



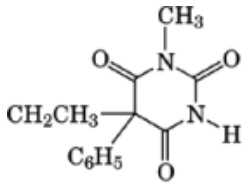
(**11**)



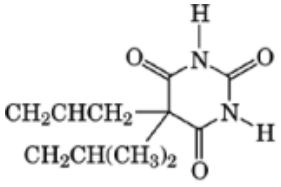
(**12**)



(13)



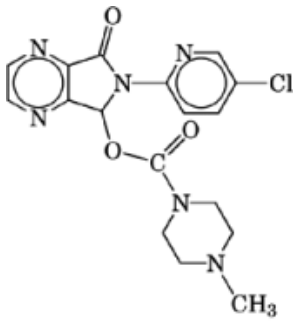
(14)



(15)

1.2.2. Benzodiazepines

The marketed benzodiazepine anxiolytics and sedative– hypnotics (see Table 2) act via agonism at benzodiazepine receptors (BZRs) within the central nervous system to yield a wide spectrum of therapeutic actions including anxiolytic, hypnotic, muscle relaxant, and anticonvulsant effects (43). The BZR is a distinct binding site on the $GABA_A$-receptor complex. The BZR can exert either positive or negative modulation on the $GABA_A$ receptor depending on the ligand. Ligands having positive allosteric modulatory activity are classified as BZR agonists. These increase the affinity of GABA to its binding site. Compounds having structures different from those of benzodiazepines can also act via the BZR, for example, the full agonists zopiclone **(16)** and zolpidem **(17)**. Figure 1 shows the synthesis of zolpidem, the first FDA approved nonbenzodiazepine hypnotic which acts via the BZR. For marketed benzodiazepines, see Table 2.



(16)

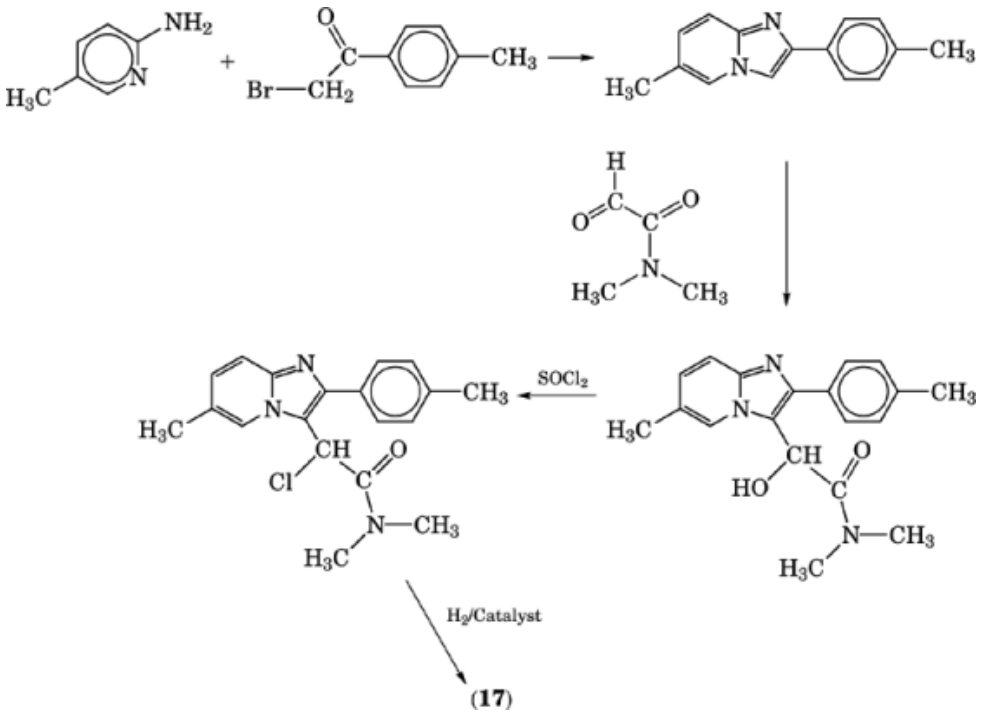
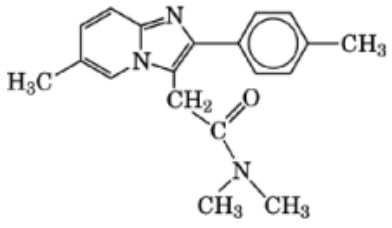


Fig. 1. Synthesis of zolpidem (**17**). 2-Amino-5-methylpyridine and 4-methylphenacyl-bromide give the imidazo[1,2-*a*]pyridine derivative which is then added to *N*,*N*-dimethyl-2-oxo-acetamide. The reaction of the adduct and $SOCl_2$ leads to a chloroacetamide derivative which is then reduced by catalytic hydrogenation to (**17**). This product is transformed into the hemitartrate salt of zolpidem (44–46).



(**17**)

Table 2. Benzodiazepines Marketed as Psychopharmacological Agents

Agent	Nomen-clature[a]	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
alprazolam	INN, BANJAN, USAN	[28981-97-7]	Xanax	$C_{17}H_{13}ClN_4$	47
bentazepam	INN, USAN	[29462-18-8]	Thiadipone, Tiadipona	$C_{17}H_{16}N_2OS$	48
bromazepam	INN, BAN, JAN, USAN	[1812-30-2]	Lexomil, Lexotan, Lexotanil	$C_{14}H_{10}BrN_3S$	49

Table 2. ***Continued***

Agent	Nomen-clature[a]	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
brotizolam	INN, BAN, JAN, USAN	[57801-81-7]	Lendorm	$C_{15}H_{10}BrClN_4O$	50
camazepam	INN	[36104-80-0]	Albego, Panevril	$C_{19}H_{18}ClN_3O_3$	51
chlordiazepoxide	INN, BAN, JAN, USAN	[58-25-3]	Librium	$C_{16}H_{14}ClN_3O$	52
chlordiazepoxide hydrochloride	BAN, JAN, USAN	[438-41-5]	Librium	$C_{16}H_{15}Cl_2N_3O$	52
cinolazepam	INN	[75696-02-5]	Gerodorm	$C_{18}H_{13}ClFN_3O_2$	53
clobazam	INN, BAN, USAN	[22316-47-8]	Frisium, Urbanyl	$C_{16}H_{13}ClN_2O_2$	54
clonazepam	INN, BAN, JAN, USAN	[1622-61-3]	Rivotril	$C_{15}H_{10}ClN_3O_3$	55
clorazepate dipotassium	INN, JAN USAN	[57109-90-7]	Tranxen(e), Tranxilium	$C_{16}H_{11}ClK_2N_2O_4$	56
clotiazepam	INN, JAN	[33671-46-4]	Clozan, Trecalmo	$C_{16}H_{15}ClN_2OS$	57
cloxazolam	INN, JAN	[24166-13-0]	Betavel, Cloxam	$C_{17}H_{14}Cl_2N_2O_2$	58
delorazepam	INN	[2894-67-9]	Briatum	$C_{15}H_{10}Cl_2N_2O$	59
diazepam	INN, BAN, JAN,USAN	[439-14-5]	Valium, Valrelease	$C_{16}H_{13}ClN_2O$	60
doxefazepam	INN	[40762-15-0]	Doxans	$C_{17}H_{14}ClFN_2O_3$	61
estazolam	INN, JAN USAN	[29975-16-4]	Nuctalon, Prosom	$C_{16}H_{11}ClFN_4$	62
ethyl loflazepate	INN, JAN	[29177-84-2]	Meilax, Victan	$C_{18}H_{14}ClFN_2O_3$	63
etizolam	INN, JAN	[40054-69-1]	Depas, Pasaden	$C_{17}H_{15}ClN_4S$	64
fludiazepam	INN, JAN	[3900-31-0]	Erispan	$C_{16}H_{12}ClFN_2O$	65
flumazenil	INN, BAN, USAN	[78755-81-4]	Anexate, Romazicon	$C_{15}H_{14}FN_3O_3$	66
flunitrazepam	INN, BAN, JAN, USAN	[1622-62-4]	Narcozep, Rohypnol Dalmadorm, Dalmane, Dalmate,	$C_{16}H_{12}FN_3O_3$	67
flurazepam	INN, BAN, JAN	[17617-23-1]	Dormodor[c]	$C_{21}H_{23}ClFN_3O$	68
flurazepam hydrochloride	USAN	[1172-18-5]		$C_{21}H_{25}Cl_3FN_3O$	68
flurazepam monohydro-chloride		[36105-20-1]		$C_{21}H_{24}Cl_2FN_3O$	68
flutazolam	INN, JAN	[27060-91-9]	Coreminal	$C_{19}H_{18}ClFN_2O_3$	69
flutemazepam	INN	[52391-89-6]	Somnal	$C_{16}H_{12}ClFN_2O_2$	
flutoprazepam	INN, JAN	[25967-29-7]	Restar, Restas	$C_{19}H_{16}ClFN_2O$	70
halazepam	INN, BAN, USAN	[23092-17-3]	Paxipam	$C_{17}H_{12}ClF_3N_2O$	71
haloxazolam	INN, JAN	[59128-97-1]	Somelin	$C_{17}H_{14}BrFN_2O_2$	72
ketazolam	INN, BAN, USAN	[27223-35-4]	Solatran, Unakalm	$C_{20}H_{17}ClN_2O_3$	73
loprazolam	INN, BAN	[61197-73-7]	Dormonoct, Somnovit	$C_{23}H_{21}ClN_6O_3$	74
loprazolam mesylate		[61197-93-1]		$C_{24}H_{25}ClN_6O_6S$	
lorazepam	INN, BAN, JAN, USAN	[846-49-1]	Ativan	$C_{15}H_{10}Cl_2N_2O_2$	75
lorazepam pivalate[d]		[57773-81-6]		$C_{29}H_{19}Cl_2N_2O_4$	75
lormetazepam	INN, BAN, JAN, USAN	[848-75-9]	Noctamid(e)	$C_{16}H_{12}Cl_2N_2O_2$	76
medazepam	INN, BAN, JAN	[2898-12-6]	Nobrium	$C_{16}H_{15}ClN_2$	77
medazepam hydrochloride	USAN	[2898-11-5]		$C_{16}H_{16}Cl_2N_2$	77
metaclazepam	INN	[65517-27-3]	Talis	$C_{18}H_{18}BrClN_2O$	78
metaclazepam hydrochloride		[61802-93-5]		$C_{18}H_{19}BrCl_2N_2O$	
mexazolam	INN, JAN	[31868-18-5]	Melex	$C_{18}H_{16}Cl_2N_2O_2$	79

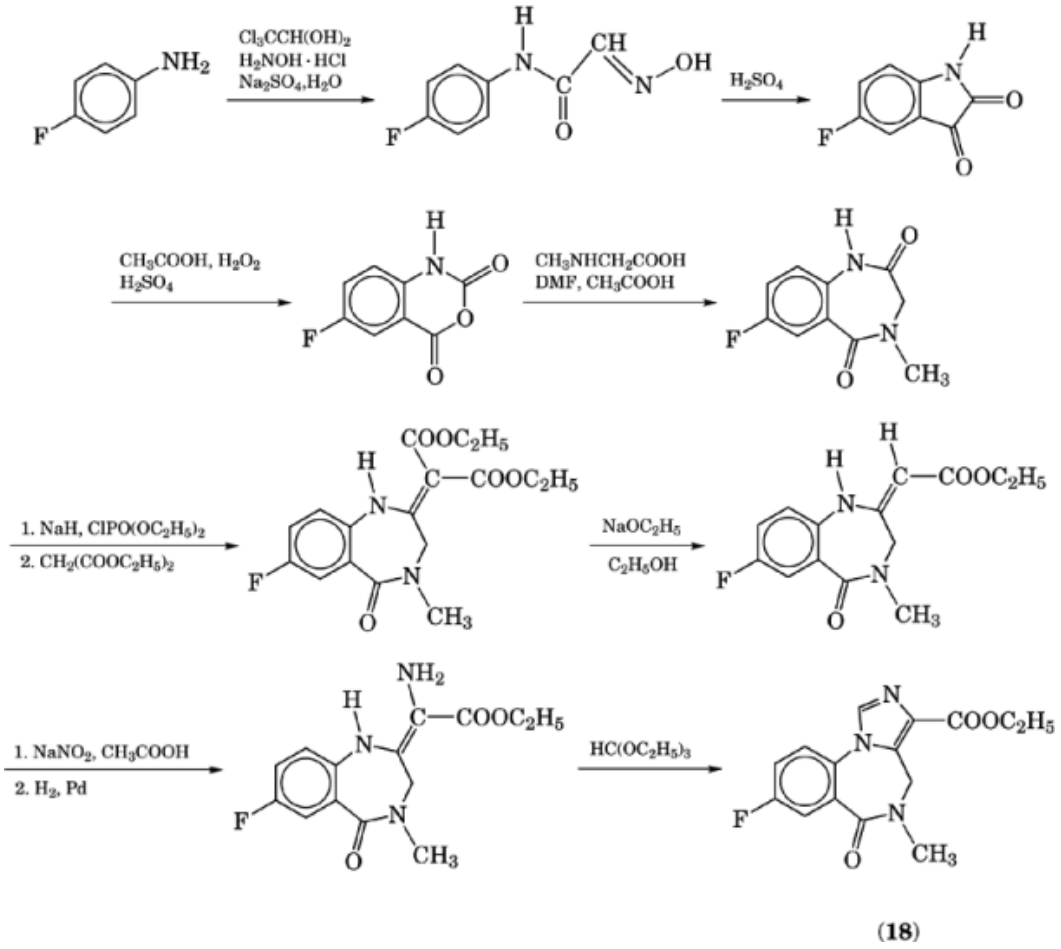
Table 2. ***Continued***

Agent	Nomen-clature[a]	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
midazolam	INN, BAN, JAN	[59467-70-8]	Dormicum, Hypnovel, Versed[e]	$C_{18}H_{13}ClFN_3$	80
midazolam hydrochloride	USAN	[59467-96-8]		$C_{18}H_{14}Cl_2FN_3$	80
midazolam maleate	USAN	[59467-94-6]		$C_{22}H_{17}ClFN_3O_4$	80
nimetazepam	INN, JAN	[2011-67-8]	Erimin	$C_{16}H_{13}N_3O_3$	81
nitrazepam	INN, BAN, JAN, USAN	[146-22-5]	Mogadon	$C_{15}H_{11}N_3O_3$	82
nordazepam	INN	[1088-11-5]	Nordaz, Vegesan	$C_{15}H_{11}ClN_2O$	83
oxazepam	INN, BAN, JAN, USAN	[604-75-1]	Adumbran, Serax	$C_{15}H_{11}ClN_2O_2$	84
oxazolam	INN, JAN	[24143-17-7]	Convertal, Quiadon	$C_{18}H_{17}ClN_2O_2$	85
phenazepam		[51753-57-2]		$C_{15}H_{10}BrClN_2O$	86
pinazepam	INN	[52463-83-9]	Domar, Duna	$C_{18}H_{13}ClN_2O$	87
prazepam	INN, BAN, JAN, USAN	[2955-38-6]	Centrax, Demetrin	$C_{19}H_{17}ClN_2O$	88
quazepam	INN, BAN, USAN	[36735-22-5]	Dormalin	$C_{17}H_{11}ClF_4N_2S$	89
temazepam	INN, BAN, USAN	[846-50-4]	Restoril	$C_{16}H_{13}ClN_2O_2$	90
tetrazepam	INN	[10379-14-3]	Musaril, Myolastan	$C_{16}H_{17}ClN_2O$	91
tofisopam	INN, JAN	[22345-47-7]	Grandaxin	$C_{22}H_{26}N_2O_4$	92
triazolam	INN, BAN, JAN, USAN	[28911-01-5]	Halcion	$C_{17}H_{12}ClN_4$	93

[a] International nonproprietary name (INN), British approved name (BAN), Japanese accepted name (JAN), and United States adopted name (USAN).
[b] Only selected salts are included. Trade names shown can represent the base or any of the salts included in "Nomenclature".
[c] Trade names for listed flurazepam agents.
[d] Also called pivazepam.
[e] Trade names for listed midazolam agents.

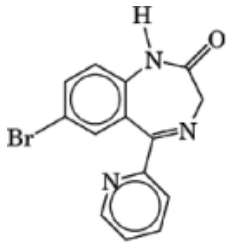
Another class of ligands called inverse agonists is found among β-carbolines and benzodiazepine derivatives. These act to depress the function of the $GABA_A$ receptor complex. None of these compounds, however, is marketed. Other BZR ligands bind to the allosteric site without inducing any appreciable alteration of the $GABA_A$ receptor gating function. However, these compounds selectively and competitively block the action of both BZR agonists and inverse agonists. Accordingly, they are named BZR antagonists. The imidazobenzodiazepine flumazenil [78755-81-4] (2) is the only representative in clinical use. Flumazenil, a specific BZR antagonist having exceptionally good tolerance and effectiveness as an antidote of mono-overdose with BZR agonists, is also used for shortening post-operational unconsciousness following anesthesia involving a BZR agonist. The synthesis of flumazenil is shown in Figure 2.

Benzodiazepines, ie, the full BZR agonists, are prescribed for anxiety, insomnia, sedation, myorelaxation, and as anticonvulsants (97). Those benzodiazepines most commonly prescribed for the treatment of anxiety disorders are lorazepam **(19)**, alprazolam **(20)**, diazepam **(21)**, bromazepam **(22)**, chlorazepate **(23)**, and oxazepam **(24)**. These drugs together represent about 70% of total

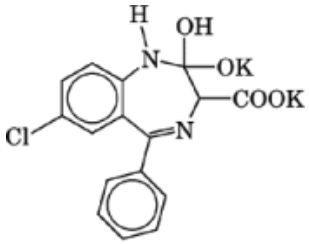


(**18**)

Fig. 2. Synthesis of flumazenil (**18**). The isonitrosoacetanilide is synthesized from 4-fluoroaniline. Cyclization using sulfuric acid is followed by oxidization using peracetic acid to the isatoic anhydride. Reaction of sarcosine in DMF and acetic acid leads to the benzodiazepine-2,5-dione. Deprotonation, phosphorylation, and subsequent reaction with diethyl malonate leads to the diester. After selective hydrolysis and decarboxylation the resulting monoester is nitrosated and catalytically hydrogenated to the aminoester. Introduction of the final carbon atom is accomplished by reaction of triethyl orthoformate to yield (**18**) (94–96).

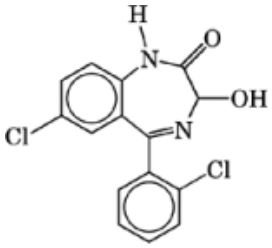


(**22**)

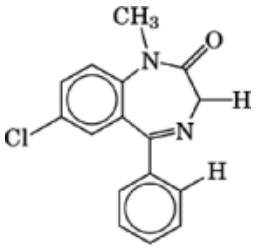


(23)

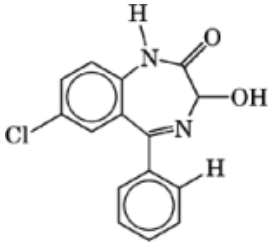
worldwide tranquilizer unit sales. Those benzodiazepines used most frequently in treating insomnia are triazolam **(25)**, temazepam **(26)**, flunitrazepam **(27)**, lormetazepam **(28)**, estazolam **(29)**, and flurazepam **(30)**, which together represent approximately one-third of total worldwide unit sales in the diverse market



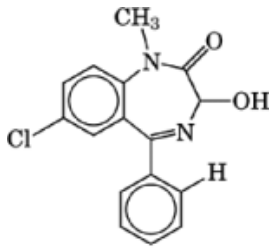
(19)



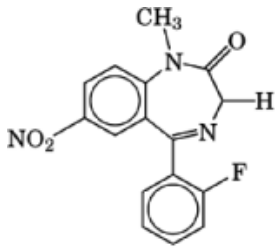
(21)



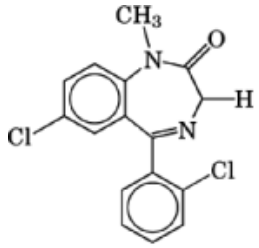
(24)



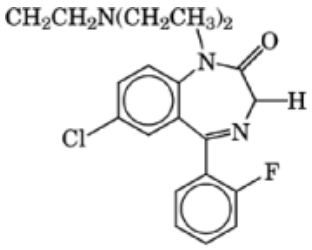
(**26**)



(**27**)

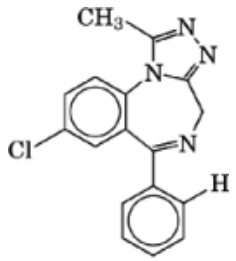


(**28**)

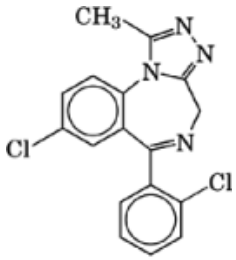


(**30**)

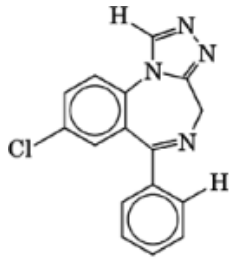
of sedative–hypnotics. Zopiclone **(16)** and zolpidem **(17)** are approved as hypnotics. Combination preparations are available for some benzodiazepines, eg, diazepam, clorazepate, chlordiazepoxide, and oxazepam. In view of the broad



(20)



(25)



(29)

therapeutic index of benzodiazepines, adverse effects can be largely avoided by optimizing dosage for an individual patient. Adverse effects of BZR agonists are primarily those related to central nervous system depression and include ataxia, myorelaxation, and drowsiness. Abuse and dependence problems can also arise. Interactions occur with ethanol and other central nervous system depressants.

1.2.3. Buspirone

Buspirone **(3)** hydrochloride has been approved for the symptomatic management of generalized anxiety disorder (Table 3). This drug is of special interest because it does not exert its therapeutic actions via modulation of the $GABA_A$ receptor complex. This compound is structurally unrelated to the benzodiazepines, barbiturates, or the other anxiolytics and sedative–hypnotics discussed. The anxiolytic effect of buspirone may result from partial agonism at the $5\text{-}HT_{1A}$ receptor, although its pharmacological profile exhibits some similarity to that of dopaminergic receptor antagonists. Antipsychotics are sometimes used to treat anxiety disorders.

The pharmacological profile of buspirone in both animals and humans differs substantially from that of the benzodiazepine anxiolytics. Buspirone lacks anticonvulsant, myorelaxant, and hypnotic effects. It also produces less sedation resulting in less psychomotor impairment in conjunction with ethanol consumption.

Table 3. Miscellaneous Anxiolytics and Sedative–Hypnotics

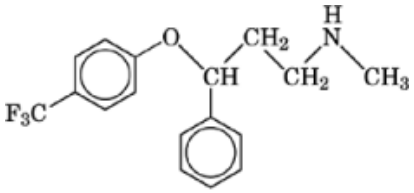
Agent	Nomen-clature[a]	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
buspirone	INN, BAN	[36505-84-7]	Bespar, Buspar	$C_{21}H_{31}N_5O_2$	98
buspirone hydrochloride	USAN	[33386-08-2]		$C_{21}H_{32}ClN_5O_2$	98
chloral hydrate	BAN, JAN, USAN	[302-17-0]	Chloradorm, Notec	$C_2H_3Cl_3O_2$	99
clomethiazole	INN[c]	[533-45-9]	Distraneurine, Heminevrin	C_6H_8ClNS	100
etomidate	INN, BAN, USAN	[33125-97-2]	Amidate	$C_{14}H_{16}N_2O_2$	101
glutethimide	INN, BAN, USAN	[77-21-4]	Doriden	$C_{13}H_{15}NO_2$	102
hydroxyzine hydrochloride	JAN, USAN	[2192-20-3]	Atarax	$C_{21}H_{29}Cl_3N_2O_2$	103
ketamine	INN, BAN	[6740-88-1]	Ketalar	$C_{13}H_{16}ClNO$	104
ketamine hydrochloride	JAN, USAN	[1867-66-9]		$C_{13}H_{17}Cl_2NO$	104
meprobamate	INN, BAN, JAN, USAN	[57-53-4]	Equanil, Miltown	$C_9H_{18}N_2O_4$	105
methaqualone	INN, BAN, USAN	[72-44-6]	Optimil, Torinal	$C_{16}H_{14}N_2O$	106
methyprylon	INN, USAN[d]	[125-64-4]	Noludar, Nolurate	$C_{10}H_{17}NO_2$	107
propofol	INN, BAN, USAN	[2078-54-8]	Diprivan	$C_{12}H_{18}O$	108
zolpidem	INN, BAN	[82626-48-0]	Ambien, Lorex, Stilnox	$C_{19}H_{21}N_3O$	109
zolpidem tartrate	USAN	[99294-93-6]		$C_{42}H_{48}N_6O_8$	109
zopiclone	INN, BAN JAN	[43200-80-2]	Imovane, Zimovane	$C_{17}H_{17}ClN_6O_3$	110

[a] International nonproprietary name (INN), British approved name (BAN), Japanese accepted name (JAN), and United States adopted name (USAN).
[b] Only selected salts are included. Trade names shown can represent the base or any of the salts included in "Nomenclature".
[c] BAN = chlormethiazole.
[d] BAN = methylprylone.

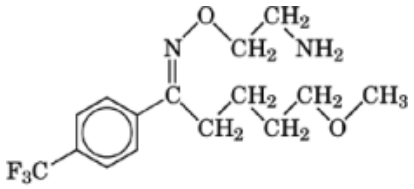
Adverse effects include headache, dizziness, nervousness, light-headedness, excitement, and nausea. A lagtime of a week or more before anxiolysis is achieved makes buspirone inappropriate for use when rapid action is required. Additionally, some evidence indicates that buspirone may be less effective than BZR agonists in treating severe anxiety or in patients having prior treatment experience with BZR agonists. Buspirone represents about 2% of total worldwide tranquilizer unit sales.

1.2.4. Selective Serotonin Reuptake Inhibitors

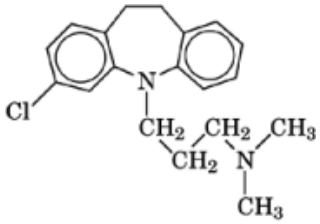
In view of the mechanism of action of selective serotonin reuptake inhibitors (SSRIs), it appears that the resulting increased availability of the neurotransmitter serotonin within the synaptic cleft is responsible for the pharmacological effects of this drug class. However, in view of the delayed onset therapeutic action of SSRIs it has been hypothesized that their therapeutic effects may, in fact, be primarily dependent on alterations in receptor density/sensitivity, changes in second messenger pathways, and/or modifications at the level of gene expression. Although originally developed and predominantly used as antidepressants, SSRIs have been increasingly used in treating panic disorder, eg, fluoxetine **(31)**, or obsessive–compulsive disorder, eg, fluvoxamine **(32)**.



(31)



(32)



(33)

SSRIs are well tolerated. Adverse effects for compounds in this class include nervousness, tremor, dizziness, headache, insomnia, sexual dysfunction, nausea, and diarrhea. In addition, the tricyclic antidepressant clomipramine **(33)**, which is a potent nonselective serotonin reuptake inhibitor, is approved for treatment of obsessive–compulsive disorder.

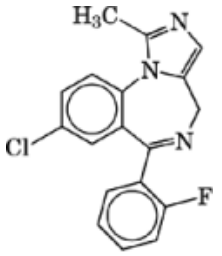
1.3. Use of Sedative–Hypnotics in General Anesthesia

In addition to use in the therapy of anxiety and insomnia, sedative–hypnotics are widely used, when given intravenously in appropriate dosages, to induce general anesthesia. Local or regional anesthesia is induced differently by agents of the cocaine class. The optimal anesthetic agent would combine unconsciousness, amnesia, analgesia, loss of both sensory and autonomic reflexes, and muscle relaxation having minimal cardiovascular and respiratory disturbance. No single anesthetic agent combines all these desired features, thus anesthesiologists often employ a cocktail of drugs.

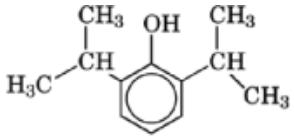
1.4. Pharmacological Profiles of Sedatives Used in Anesthesiology

Anesthetic management of a surgical patient includes premedication, induction, maintenance, emergence, and recovery. Light premedication provides sedation, decreased anxiety, amnesia, and decreased parasympathetic outflow. Oral or parenteral benzodiazepines are sedative–hypnotics used preoperatively for premedication when strong analgesia is not required. The rapid onset of action of intravenous anesthetics makes them ideally suited for induction of anesthesia. Agents having a short half-life such as midazolam **(34)** and propofol **(35)** are

often used as maintenance anesthetics. Anesthetics can also be administered in combination with intravenous narcotics to obtain appropriate levels of analgesia.



(34)



(35)

Combinations of barbiturates and benzodiazepine tranquilizers or even antihistaminergics having sedative properties are sometimes used. Furthermore, infusion of anesthetics can be used to provide long-term anesthesia for intensive care medicine. The antagonist flumazenil (2) is available to reverse the effects of anesthetics of the benzodiazepine class.

1.4.1. Barbiturates

The ultrashort-acting barbiturates (see Table 1) methohexital **(4)**, thiopental **(5)**, and thiamylal **(6)** are used for induction and maintenance of anesthesia. Their mechanism of pharmacological action at the $GABA_A$ receptor has been described. Barbiturates exhibit a relatively low therapeutic ratio and provide no protection against painful stimuli. They are often given in combination with other anesthetics. Thiopental is widely used owing to the rapidity with which patients pass through the stages of anesthesia. Apnea is usually the first sign of overdose. Cardiovascular depression may occur after intravenous bolus administration of barbiturates.

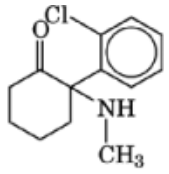
1.4.2. Benzodiazepines

Benzodiazepine derivatives (see Table 2) have gained popularity as intravenous anesthetics because of their limited effects on the cardiovascular and respiratory systems. Intravenous benzodiazepines can be used alone for minor procedures causing discomfort but not pain (eg, endoscopy), or in combination with local anesthetics. Midazolam is the most widely utilized benzodiazepine in intravenous anesthesia. Midazolam **(34)** is a BZR full agonist. It has a short plasma elimination half-life, is water soluble, and has marked amnestic and anxiolytic properties. Diazepam **(21)**, lorazepam **(19)**, and flunitrazepam **(27)** are less widely used than midazolam intravenously owing to poor water solubility, slower onset, occasional pain during injection, and slower recovery.

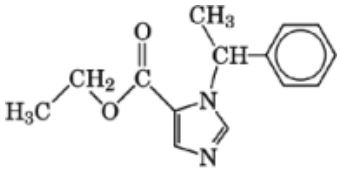
1.4.3. Other Sedative Agents

Propofol **(35)** (see Table 3) is a rapidly acting phenol derivative having a short recovery time which readily penetrates the brain. It is very lipid soluble and almost insoluble in water so it is formulated in a fat emulsion.

Propofol lacks appreciable amnestic, anxiolytic, or analgesic effects. There is sometimes pain upon injection of the emulsion formulation and anesthesia induction using propofol can reduce blood pressure. Propofol has been hypothesized to act via allosteric modulation of brain $GABA_A$ and glycine receptors (111), as well as on Na^+ and K^+ channels in nerve membranes and directly on membrane lipids (112). Ketamine **(36)** induces dissociative anesthesia, ie, profound analgesia in the absence of sleep, and no loss of protective reflexes and little cardiovascular depression. Unpleasant dreams and post-operative hallucinations are serious disadvantages of ketamine, but these can be reduced by concomitant use of a benzodiazepine or an opiate. Anesthesia using ketamine is rapid and of short duration. Etomidate **(37)** induces short-lasting anesthesia without analgesia so that supplementary analgesic premedication is usually needed. Its use is confined to induction and brief procedures owing to adverse inhibition of adrenocortical steroidogenesis upon prolonged infusion.



(36)



(37)

Improved anxiolytics, hypnotics, and sedatives are expected to continue to be introduced. Future improvements in symptomatic therapy are expected to occur in increasingly modest increments. The therapeutic efficacy of benzodiazepines in generalized anxiety disorder, as well as stress-induced and situational anxiety, is well established and potential benefits in panic and phobic disorders are judged increasingly positively (113). Benzodiazepine receptor agonists, both benzodiazepines and nonbenzodiazepines, continue to be the predominant prescription drugs used to treat insomnia. Proper dosage and treatment duration can considerably reduce the undesirable effects of drugs acting as agonists at BZRs, ie, sedation, ethanol potentiation, abuse liability, and physical dependence. The potential advantages offered by the BZR partial agonist approach could represent an important advance by maintaining full therapeutic efficacy while further minimizing undesirable effects. Clinical investigations carried out in anxiety and sleep disorders using such BZR partial agonists as divaplon [90808-12-1], saripidem [103844-86-6], and abecarnil [111841-85-1] are expected to provide the basis for such an evaluation.

The possibility of the existence of subtypes of $GABA_A$ receptors differentially sensitive to BZR ligands and exhibiting differential involvement in neuronal populations responsible for anxiety, sleep, or sedation versus undesired drug effects remains a promising avenue which could yield an improved therapeutic index. The clinical introduction of buspirone **(3)** has emphasized the potential value of mechanisms other than those based on $GABA_A$ receptor function as a way of achieving anxiolytic activity. As of 1996, a number of related compounds acting through 5-HT_{1A} receptor partial agonism and antagonism were in various stages of clinical development for this indication. Furthermore, exploratory approaches focusing on cholecystokinin receptor antagonism, 5-HT_2 receptor antagonism, 5-HT_3 receptor antagonism, neuropeptide Y_1 receptor agonism, neuronal nicotinic

acetylcholine receptor subtype agonism, melatonin receptor agonism, *N*-methyl-D-aspartate receptor antagonism, as well as neurosteroids (eg, epalons) as the basis of novel treatment strategies for anxiety disorders and/or insomnia were actively being followed preclinically and even in clinical investigations (114). Finally, increasing attention is being given to the positive results from clinical investigations of various marketed antidepressants, eg, tricyclics and monoamine–oxidase inhibitors, in panic disorder and phobias (115).

2. Antidepressants

Depression is a common psychiatric disorder. The lifetime risk of developing a depressive episode is estimated to be as high as 8–12% for men and 20–26% for women (116). Depression, one of the most widespread of all life-threatening disorders, is almost always a factor in the more than 30,000 suicides that occur annually in the United States alone (117).

2.1. Classification of Depressive Disorders

The most common mood disorders are major or unipolar depression and manic–depressive illness or bipolar depression. There are other affective disorders, such as dysthymia, which are generally treated with available antidepressants. Major depression is characterized by symptoms such as depressed mood, diminished interest or pleasure in nearly all activities, decreased appetite with weight loss, fatigue, loss of energy, feelings of worthlessness, diminished ability to concentrate, and recurrent thoughts of death or suicidal ideation (118). In contrast, manic episodes are characterized by expansive mood, grandiosity, inflated self-esteem, pressured speech, flight of ideas, and poverty of sleep. The symptomatology of depression is often complicated by the presence of other psychiatric disorders such as anxiety and psychosis.

2.2. Pharmacological Profiles of Antidepressants

Depression is believed to result from a decreased neurotransmission, ie, a lack of sufficient noradrenaline [51-41-2], serotonin [50-67-9], and/or dopamine [51-61-6] concentration at critical synapses in the brain, particularly within the limbic system. This led to the catecholamine and indoleamine hypotheses of depression. The various classes of antidepressant treatments, by blocking transmitter uptake by the neuron, or by slowing down their degradation, can increase neurotransmitter concentration to a normal level and consequently ameliorate depression (119). In the past, amphetamine [300-62-9] (amfetamine is INN) was sometimes used to treat depression, but tolerance develops to its mood-elevating effects and it has high addictive liability, potential to induce agitation, and can worsen somatic and neurovegetative symptoms of depression. Amphetamine acts via stimulation of dopamine, and to a lesser extent noradrenaline, release from neurons and concomitantly via the blockade of reuptake and metabolism by monoamine–oxidase of these two catecholamines. There are no compelling clinical data which demonstrate efficacy of psychostimulants such as amphetamine, methylphenidate, or pemoline in treating depression (120). It has also been speculated that other neurotransmitters and neuromodulators, such as neuropeptides and prostaglandins (qv), may also be involved in the etiology of depressive disorders.

Antidepressant therapy is usually associated with a delay of up to about two to three weeks before the onset of a clear beneficial effect. Therefore, it seems unlikely that the acute biochemical effects of antidepressants are responsible for the actual therapeutic response to these agents. It seems more probable that the action of antidepressants results from an adaptative process to long-term exposure to the drugs, ie, down- or up-regulation of receptor density, receptor sensitivity, second messenger pathways, and/or gene expression.

2.3. Treatment of Major Depression

Drugs commonly used for the treatment of depressive disorders can be classified heuristically into two main categories: first-generation antidepressants with the tricyclic antidepressants (TCAs) and the irreversible, nonselective monoamine–oxidase (MAO) inhibitors, and second-generation antidepressants with the atypical antidepressants, the reversible inhibitors of monoamine–oxidase A (RIMAs), and the selective serotonin reuptake inhibitors (SSRIs). Table 4 lists the available antidepressants.

Table 4. Marketed Antidepressants

Agent	Nomen-clature[a]	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
amfebutamone	INN[c]	[34911-55-2]	Wellbutrin	$C_{13}H_{18}ClNO$	123
bupropion hydrochloride	USAN	[31677-93-7]		$C_{13}H_{19}Cl_2NO$	
amineptine	INN	[57574-09-1]	Survector, Directim, Maneon	$C_{22}H_{27}NO_2$	124
amitriptyline	INN, BAN	[50-48-6]	Laroxyl, Loxaryl	$C_{20}H_{23}N$	125
amitriptyline hydrochloride	JAN, USAN	[549-18-8]		$C_{20}H_{24}ClN$	
amoxapine	INN, BAN, JAN, USAN	[14028-44-5]	Asendin, Demolox, Moxadil	$C_{17}H_{16}ClN_3O$	126
butriptyline	INN, BAN	[35941-65-2]	Evadene,	$C_{21}H_{27}N$	127
butriptyline hydrochloride	USAN	[5585-73-9]	Evadyne	$C_{21}H_{28}ClN$	127
citalopram	INN, BAN	[59729-33-8]	Cipramil, Seropram	$C_{20}H_{21}FN_2O$	128
clomipramine	INN, BAN	[303-49-1]	Anafranil,	$C_{19}H_{23}ClN_2$	129
clomipramine hydrochloride	USAN, JAN	[17321-77-6]	Hydiphen	$C_{19}H_{24}Cl_2N_2$	129
demexiptiline	INN	[24701-51-7]	Deparon, Tinoran	$C_{18}H_{18}N_2O$	130
desipramine	INN, BAN	[50-47-5]	Norpramin,	$C_{18}H_{22}N_2$	131
desipramine hydrochloride	USAN, JAN	[58-28-6]	Pertofran(e)	$C_{18}H_{23}ClN_2$	131
dosulepin	INN[d]	[113-53-1]	Prothiaden,	$C_{19}H_{21}NS$	132
dothiepin hydrochloride	USAN	[897-15-4]	Tihilor	$C_{19}H_{22}ClNS$	132
doxepin	INN, BAN	[1668-19-5]	Adapin,	$C_{19}H_{21}NO$	133
doxepin hydrochloride	USAN	[1229-29-4]	Quitaxon, Sinequan	$C_{19}H_{22}ClNO$	133
fluoxetine	INN, BAN, USAN	[54910-89-3]	Prozac	$C_{17}H_{18}F_3NO$	134
fluoxetine hydrochloride	USAN	[59333-67-4]	Prozac	$C_{17}H_{19}ClF_3NO$	134
fluvoxamine	INN, BAN	[54739-18-3]	Fevarin, Floxyfral	$C_{15}H_{21}F_3N_2O_2$	135
imipramine	INN, BAN	[50-49-7]	Tofranil	$C_{19}H_{24}N_2$	136
imipramine hydrochloride	JAN, USAN	[113-52-0]		$C_{19}H_{25}ClN_2$	
indalpine	INN, BAN	[63758-79-2]	Upstene	$C_{15}H_{20}N_2$	137
iprindole	INN, BAN, USAN	[5560-72-5]	Prondol, Tertran	$C_{19}H_{28}N_2$	138
iproclozide	INN, BAN	[3544-35-2]	Iproclozide, Sursum	$C_{11}H_{15}ClN_2O_2$	139
iproniazid	INN, BAN	[54-92-2]	Ipronid, Marsilid	$C_9H_{13}N_3O$	140
isocarboxazid	INN, BAN, USAN	[59-63-2]	Marplan	$C_{12}H_{13}N_3O_2$	141
lofepramine	INN, BAN	[23047-25-8]	Gamanil,	$C_{26}H_{27}ClN_2O$	142
lofepramine hydrochloride	JAN, USAN	[26786-32-3]	Tymelyt	$C_{26}H_{28}Cl_2N_2O$	142
maprotiline	INN, BAN, USAN	[10262-69-8]	Ludiomil	$C_{20}H_{23}N$	143
maprotiline hydrochloride	JAN, USAN	[10347-81-6]	Ludiomil	$C_{20}H_{24}ClN$	143
metapramine	INN	[21730-16-5]	Prodastene, Timaxel	$C_{16}H_{18}N_2$	144
mianserin	INN, BAN	[24219-97-4]	Bolvidon, Tolvon	$C_{18}H_{20}N_2$	145
mianserin hydrochloride	USAN, JAN	[21535-47-7]		$C_{18}H_{21}ClN_2$	
milnacipran	INN	[92623-85-3]	Dalcipran	$C_{15}H_{22}N_2O$	146

Table 4. ***Continued***

Agent	Nomen-clature[a]	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
minaprine	INN, BAN, USAN	[25905-77-5]	Cantor, Caprim,	$C_{17}H_{22}N_4O$	147
minaprine dihydro-chloride	USAN	[25953-17-7]	Isopulsan	$C_{17}H_{24}Cl_2N_4O$	147
mirtazapine	INN, BAN, USAN	[61337-67-5]	Remergon	$C_{17}H_{19}N_3$	148
moclobemide	INN, BAN USAN	[71320-77-9]	Aurorix, Manerix, Moclamine	$C_{13}H_{17}ClN_2O_2$	149
nefazodone	INN, BAN	[83366-66-9]	Dutonin,	$C_{25}H_{32}ClN_5O_2$	150
nefazodone hydrochloride	USAN	[82752-99-6]	Serzone	$C_{25}H_{33}Cl_2N_5O_2$	150
nialamide	INN, BAN	[51-12-7]	Niamid, Nuredal, Surgex	$C_{16}H_{18}N_4O_2$	151
nortriptyline	INN, BAN	[72-69-5]	Allegron, Aventyl, Pamelor	$C_{19}H_{21}N$	152
nortriptyline hydrochloride	JAN, USAN	[894-71-3]		$C_{19}H_{22}ClN$	
noxiptiline	INN[e]	[3362-45-6]	Agedal, Elronon, Sipcar	$C_{19}H_{22}N_2O$	153
opipramol dihydro-chloride	INN, BAN	[315-72-0]	Ensidon,	$C_{23}H_{29}N_3O$	154
opipramol dihydro-chloride	USAN	[909-39-7]	Oprimol	$C_{23}H_{31}Cl_2N_3O$	154
paroxetine	INN, BAN, USAN	[61869-08-7]	Paxil, Seroxat, Tagonis	$C_{19}H_{20}FNO_3$	155
phenelzine	INN, BAN	[51-71-8]	Kalgan,	$C_8H_{12}N_2$	156
phenelzine sulfate	USAN	[156-51-4]	Nardil	$C_8H_{14}N_2O_4S$	156
pirlindole	INN	[60762-57-4]	Lifril, Pyrazidol	$C_{15}H_{18}N_2$	157
propizepine	INN	[10321-12-7]	Depressin, Vagran	$C_{17}H_{20}N_4O$	158
protriptyline	INN, BAN	[438-60-8]	Concordin, Triptil, Vivactil	$C_{19}H_{21}N$	159
protriptyline hydrochloride	USAN	[1225-55-4]		$C_{19}H_{22}ClN$	
quinupramine	INN	[31721-17-2]	Kevopril, Kinupril	$C_{21}H_{24}N_2$	160
sertraline	INN, BAN	[79617-96-2]	Lustral, Zoloft	$C_{17}H_{17}Cl_2N$	161
sertraline hydrochloride	USAN	[79559-97-0]		$C_{17}H_{18}Cl_3N$	
setiptiline	INN	[57262-94-9]	Tecipul	$C_{19}H_{19}N$	162
tianeptine	INN	[66981-73-5]	Stablon	$C_{21}H_{25}ClN_2O_4S$	163
toloxatone	INN	[29218-27-7]	Humoryl	$C_{11}H_{13}NO_3$	164
tranylcypromine	INN, BAN	[155-09-9]	Parnate, Parnitene	$C_9H_{11}N$	156
trazodone	INN, BAN	[19794-93-5]	Desyrel, Molipaxin	$C_{19}H_{22}ClN_5O$	165
trazodone hydrochloride	JAN, USAN	[25332-39-2]		$C_{19}H_{23}Cl_2N_5O$	
trimipramine	INN, BAN, USAN	[739-71-9]	Stangyl,	$C_{20}H_{26}N_2$	166
trimipramine maleate	JAN, USAN	[521-78-8]	Surmontil	$C_{24}H_{30}N_2O_4$	166
venlafaxine	INN, BAN	[93413-69-5]	Effexor	$C_{17}H_{27}NO_2$	167
venlafaxine hydrochloride	USAN	[99300-78-4]		$C_{17}H_{28}ClNO_2$	
viloxazine	INN, BAN	[46817-91-8]	Emovil, Vialan, Vivalan	$C_{13}H_{19}NO_3$	168
viloxazine hydrochloride	USAN	[35604-67-2]		$C_{13}H_{20}ClNO_3$	

[a] International nonproprietary name (INN), British approved name (BAN), Japanese accepted name (JAN), and United States adopted name (USAN).

[b] Only selected salts are included. Trade names shown can represent the base or any of the salts included in "Nomenclature".

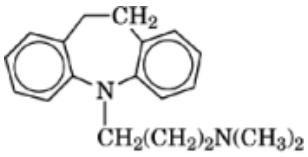
[c] BAN = bupropion.

[d] BAN = dothiepin.

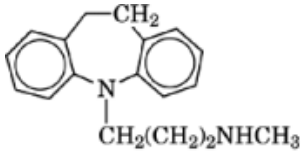
[e] BAN = noxiptylene.

2.3.1. First-Generation Antidepressants

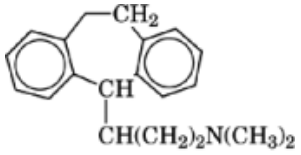
2.3.1.1. Tricyclic Antidepressants. Imipramine **(38)** was introduced in the late 1950s as one of the first pharmacotherapies for depression. At that time, chlorpromazine [50-53-3] was the first effective antipsychotic treatment to be discovered. Researchers looked for similar chemical structures and imipramine was found to be effective in the symptomatic treatment of depression. Over the years, other congeners, such as desipramine **(39)**, amitriptyline **(40)**, and dothiepin **(41)**, were synthesized and shown to be clinically efficacious antidepressant drugs (121). These substances, known under the general rubric of tricyclic antidepressants, share a basic chemical structure comprising



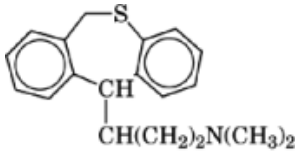
(38)



(39)



(40)

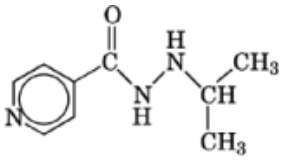


(41)

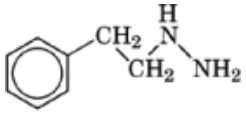
a three-ring core. TCAs remain the mainstay of treatment for depression which represent more than half of total worldwide antidepressant unit sales, despite drawbacks such as anticholinergic side effects, ie, blurred vision, dry mouth, constipation, or confusion; cardiovascular side effects, ie, postural hypotension, dizziness, hypertension, or antiarrhythmic effect; sedation; and weight gain.

2.3.1.2. Monoamine–Oxidase Inhibitors. In the mid-1950s, tuberculosis patients with depression being treated with iproniazid **(42)** were occasionally reported to become euphoric. This observation led to the discovery of irreversible monoamine–oxidase (MAO) inhibiting properties. Hydrazine and nonhydrazine-related MAO inhibitors were subsequently shown to be antidepressants (122). Three other clinically effective irreversible

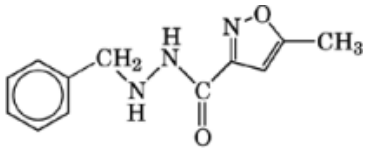
MAO inhibitors have been approved for treatment of major depression: phenelzine **(43)**, isocarboxazid **(44)**, and tranylcypromine **(45)**.



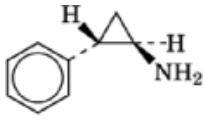
(42)



(43)



(44)



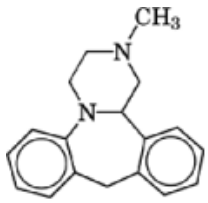
(45)

Chronic use of these irreversible MAO inhibitors has been associated with life-threatening toxicity, ie, hepatotoxicity and hypertensive crisis. Interactions with tyramine contained in food and other drugs have severely limited use of irreversible MAO inhibitors. These MAO inhibitors are also nonselective, inhibiting both MAO-A and MAO-B isoenzymes. Furthermore, they interfere with the hepatic metabolism of many drugs.

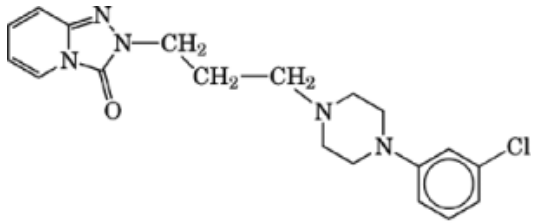
2.3.2. Second-Generation Antidepressants

The frequency of adverse effects associated with first-generation antidepressants and the lack of patient compliance arising from such adverse effects led to the development of a number of second-generation antidepressants.

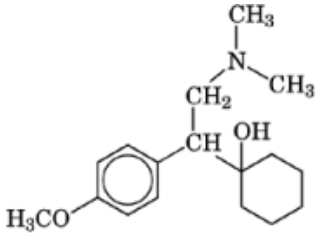
2.3.2.1. Atypical Antidepressants. Structurally diverse drugs such as the tetracyclic mianserin **(46)** and various bicyclic and tricyclic compounds such as trazodone **(47)**, venlafaxine **(48)**, nefazodone **(49)**, and amfebutamone **(50)** are atypical antidepressants. The exact mechanism of action is unclear but probably



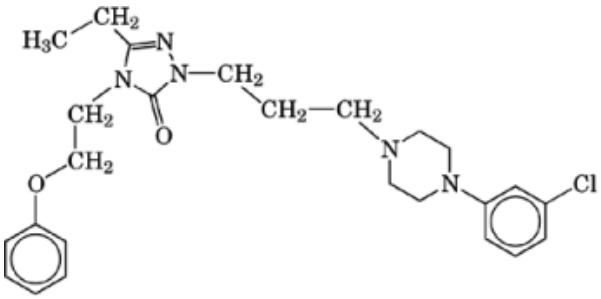
(46)



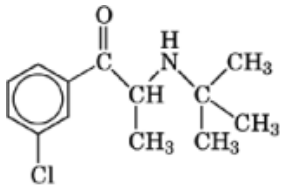
(47)



(48)



(49)



(50)

involves actions at serotonin, noradrenaline, and/or dopamine synapses (169). Such drugs exhibit reduced toxicity, improved patient compliance, and lower toxicity in overdose than first-generation antidepressants.

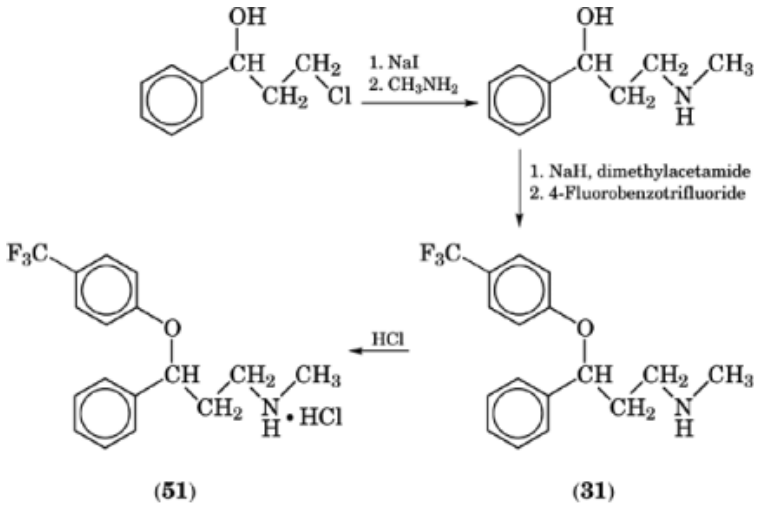
Amfebutamone **(50)** (bupropion) is an antidepressant drug that is structurally and mechanistically different from the agents previously approved for treating this disorder. It exhibits a greater effect on the neuronal reuptake of dopamine than on other biogenic amines even though this property does not seem to, by itself, account for its antidepressant effects. In clinical studies, it was found to be as effective as the standard drugs used in the treatment of major depression, but has fewer side effects. It is reported to be particularly useful in patients resistant to other agents, as well as in patients with atypical depression. It is not sedating or cardiotoxic and does not exhibit anticholinergic effects or produce weight gain. Potential adverse effects include seizures and psychosis.

Nefazodone **(49)** is a phenylpiperazine derivative exhibiting a pharmacological profile that is distinct from that of first-generation agents, as well as the more selectively acting second-generation agents, ie, serotonin or noradrenaline reuptake inhibitors. Nefazodone acts both as a serotonin receptor type 2 antagonist and as a serotonin reuptake inhibitor. It appears to be free of cardiotoxicity and is well tolerated even at high doses. It lacks the typical anticholinergic side effects of the tricyclic antidepressants, as well as serotonergic and noradrenergic mediated side effects.

Venlafaxine **(48)** is a structurally novel phenylethylamine derivative that strongly inhibits both noradrenaline and serotonin reuptake. It lacks anticholinergic, antihistaminergic, and antiadrenergic side effects. As compared to placebo, most common adverse events are nausea, somnolence, dizziness, dry mouth, and sweating. Venlafaxine-treated patients also experienced more headaches and nausea, but less dry mouth, dizziness, and tremor than patients treated with comparator antidepressants.

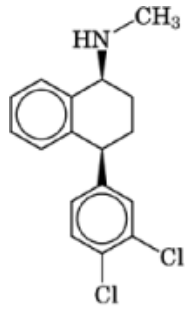
2.3.2.2. Selective Serotonin Reuptake Inhibitors. Serotonin plays a pivotal role in the physiological regulation of mood. The selective serotonin reuptake inhibitors (SSRIs) resulted from an effort by the pharmaceutical companies to develop drugs exhibiting a higher degree of selectivity for the central serotonin transporter (170). Owing to serotonergic uptake blocking properties, a net enhancement of serotonergic function results from the administration of SSRIs. The drug fluoxetine **(31)**, the first SSRI approved by the U.S. Food and Drug Administration for the treatment of major depression, was rapidly followed by several other SSRIs. The synthesis of fluoxetine (Prozac), marketed as a racemate and the commercially most important antidepressant, is shown in Figure 3.

SSRIs are widely used for treatment of depression, as well as, for example, panic disorders and obsessive–compulsive disorder. These drugs are well recognized as clinically effective antidepressants having an improved side-effect profile as compared to the TCAs and irreversible MAO inhibitors. Indeed, these drugs lack the anticholinergic, cardiovascular, and sedative effects characteristic of TCAs. Their main adverse effects include nervousness/anxiety, nausea, diarrhea or constipation, insomnia, tremor, dizziness, headache, and sexual dysfunction. The most commonly prescribed SSRIs for depression are fluoxetine **(31)**, fluvoxamine **(32)**, sertraline **(52)**, citalopram **(53)**, and paroxetine **(54)**. SSRIs together represent about one-fifth of total worldwide antidepressant unit sales.

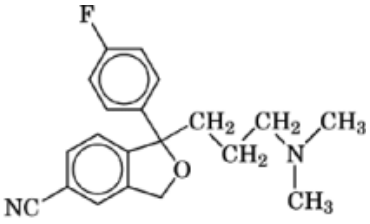


(**51**) (**31**)

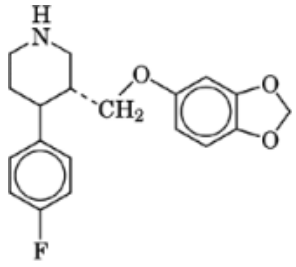
Fig. 3. Synthesis of fluoxetine (**31**). 3-Chloro-1-phenyl-1-propanol reacts with sodium iodide to afford the corresponding iodo derivative, followed by reaction with methylamine, to form 3-(methylamino)-1-phenyl-1-propanol. To the alkoxide of this product, generated using sodium hydride, 4-fluorobenzotrifluoride is added to yield after work-up the free base of the racemic fluoxetine (**31**), thence transformed to the hydrochloride (**51**) (171–174).



(**52**)

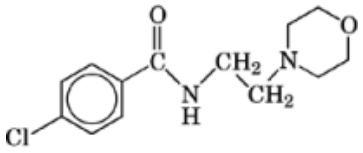


(**53**)



(54)

2.3.2.3. Reversible Inhibitors of Monoamine Oxidase. Selective MAO-A inhibitors, which are reversible (so-called RIMAs), have also been developed, therefore substantially reducing the potential for food and drug interactions. Indeed, the tyramine-potentiating effects of these drugs is much reduced compared with the irreversible MAO inhibitors. The RIMAs represent effective and safer alternatives to the older MAO inhibitors. The only marketed RIMAs are toloxatone [29218-27-7] and moclobemide **(55)**. The latter is used widely as an effective, well-tolerated antidepressant.



(55)

The second-generation antidepressants, particularly RIMAs and SSRIs, are much less toxic in overdose than the older TCAs and irreversible MAO inhibitors. However, similar to first-generation antidepressants, the therapeutic effect only becomes manifest after several weeks. Up to one-third of depressed patients are nonresponders. Ideally, an antidepressant would combine a more rapid onset of action with greater clinical efficacy and a higher responder rate, as well as even better tolerability.

2.4. Treatment of Manic–Depressive Illness

Since the 1960s, lithium carbonate [10377-37-4] and other lithium salts have represented the standard treatment of mild-to-moderate manic–depressive disorders (175). It is effective in about 60–80% of all acute manic episodes within one to three weeks of administration. Lithium ions can reduce the frequency of manic or depressive episodes in bipolar patients providing a mood-stabilizing effect. Patients are maintained on low, stabilizing doses of lithium salts indefinitely as a prophylaxis. However, the therapeutic index is low, thus requiring monitoring of serum concentration. Adverse effects include tremor, diarrhea, problems with eyes (adaptation to darkness), hypothyroidism, and cardiac problems (bradycardia–tachycardia syndrome).

Lithium ions are hypothesized to act by reducing the coupling between receptors and their G-proteins. Because several neurotransmitter receptors share common G-protein-regulated second-messenger signaling systems, lithium ions could simultaneously correct the alterations at synapses associated with depression and mania by a single action on the function of specific G-proteins. Lithium ions might also act via their interruption of the phosphatidylinositide cycle, leading to a depletion of membrane inositol and phosphoinositide-derived second-messenger products, thereby reducing signaling through those receptor systems dependent on the formation of these products. The antiepileptic valproic acid [99-66-1] and its salts have also been reported to

be therapeutically useful in treating mania (176), possibly via enhancement of GABA metabolism in the brain. Valproate semisodium [76584-70-8] (divalproex sodium) has been approved in the United States for treatment of manic episodes associated with bipolar depression.

Other agents are also used for the treatment of manic–depressive disorders based on preliminary clinical results (177). The antiepileptic carbamazepine [298-46-4] has been reported in some clinical studies to be therapeutically beneficial in mild-to-moderate manic depression. Carbamazepine treatment is used especially in bipolar patients intolerant to lithium or nonresponders. A majority of lithium-resistant, rapidly cycling manic–depressive patients were reported in one study to improve on carbamazepine (178). Carbamazepine blocks noradrenaline reuptake and inhibits noradrenaline exocytosis. The main adverse events are those found commonly with antiepileptics, ie, vigilance problems, nystagmus, ataxia, and anemia, in addition to nausea, diarrhea, or constipation. Carbamazepine can be used in combination with lithium. Several clinical studies report that the calcium channel blocker verapamil [52-53-9], registered for angina pectoris and supraventricular arrhythmias, may also be effective in the treatment of acute mania. Its use as a mood stabilizer may be unrelated to its calcium-blocking properties. Verapamil also decreases the activity of several neurotransmitters. Severe manic depression is often treated with antipsychotics or benzodiazepine anxiolytics.

2.5. Future Outlook for Antidepressants

Third-generation antidepressants are expected to combine superior efficacy and improved safety, but are unlikely to reduce the onset of therapeutic action in depressed patients (179). Many drugs in clinical development as antidepressive agents focus on established properties such as inhibition of serotonin, dopamine, and/or noradrenaline reuptake, agonistic or antagonistic action at various serotonin receptor subtypes, presynaptic α_2-adrenoceptor antagonism, or specific monoamine–oxidase type A inhibition. Examples include buspirone **(3)** (only approved for treating anxiety disorders) and ipsapirone [95847-70-4], acting as 5-HT_{1A} receptor partial agonists. Antagonism at 5-$HT_{1B/1D}$ receptors is another approach being pursued.

Modulation of second-messenger pathways is also an attractive target upon which to base novel antidepressants. Rolipram [61413-54-5], an antidepressant in the preregistration phase, enhances the effects of noradrenaline though selective inhibition of central phosphodiesterase, an enzyme which degrades cyclic adenosine monophosphate (cAMP). Modulation of the phosphatidyl inositol second-messenger system coupled to, for example, 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptors might also lead to novel antidepressants, as well as to alternatives to lithium for treatment of mania. Novel compounds such as inhibitors of *S*-adenosyl-methionine or central catechol-*O*-methyltransferase also warrant attention.

Neuropeptides also represent innovative targets for drug design in the antidepressant field. A well-known finding in biological psychiatry is hyperactivity of the hypothalamo–pituitary–adrenal axis in patients with endogenous depression. Thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and adrenocorticotropic hormone (ACTH) are hypothesized to be involved in the etiology of depression (see Hormones). Therefore, modulators of these neuropeptide receptors may represent interesting opportunities for novel antidepressants. Another tripeptide, melanocyte-stimulating hormone-release inhibiting factor-1 (MIF-1), has been claimed to be rapidly effective in the treatment of depressive illness. A number of other compounds such as calcium antagonists, *N*-methyl-D-aspartate receptor antagonists, vasopressin and melatonin receptor ligands, angiotensin-converting enzyme inhibitors, and adenosine receptor antagonists have been reported to exhibit antidepressant-like properties in animal models and thus provide drug targets worthy of study.

3. Antipsychotics

Schizophrenia is perhaps the most debilitating psychiatric illness in modern medicine, affecting about 1% of the general population. Many of those affected require institutionalization (180). Unfortunately, the compounds

available to treat this disorder are not fully effective in treating the spectrum of symptoms in all patients. Adverse effects are also a problem (181). In addition, available antipsychotic (neuroleptic) drugs (Table 5) can at most only provide symptomatic relief.

Table 5. Marketed Antipsychotics

Agents	Nomen-clature[a]	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
acetophenazine	INN	[2751-68-0]	Tindal	$C_{23}H_{29}N_3O_2S$	182
acetophenazine maleate	USAN	[5714-00-1]		$C_{31}H_{37}N_3O_{10}S$	
amisulpride	INN	[71675-85-9]	Solian	$C_{17}H_{27}N_3O_4S$	183
benperidol	INN, BAN, USAN	[2062-84-2]	Glianimon	$C_{22}H_{24}FN_3O_2$	184
bromperidol	INN, BAN, JAN, USAN	[10457-90-6]	Impromen	$C_{21}H_{23}BrFNO_2$	185
bromperidol decanoate	BAN, USAN	[75067-66-2]	Impromen	$C_{31}H_{41}BrFNO_3$	185
chlorpromazine	INN, BAN, USAN	[50-53-3]	Largactil,	$C_{17}H_{19}ClN_2S$	186
chlorpromazine hydrochloride	INN, BAN, JAN, USAN	[69-09-0]	Thorazine	$C_{17}H_{20}Cl_2N_2S$	186
chlorprothixene	INN, BAN, JAN, USAN	[113-59-7]		$C_{18}H_{18}ClNS$	
chlorprothixene acetate		[58889-16-0]	Taractan, Truxal	$C_{20}H_{22}ClNO_2S$	182
chlorprothixene hydrochloride	JAN	[6469-93-8]		$C_{18}H_{19}Cl_2NS$	
clopenthixol	INN, BAN, USAN	[982-24-1]	Sordinol	$C_{22}H_{25}ClN_2OS$	187
clotiapine	INN, JAN[c]	[2058-52-8]	Entumin, Etumina	$C_{18}H_{18}ClN_3S$	188
clozapine	INN, BAN, USAN	[5786-21-0]	Leponex, Clozaril	$C_{18}H_{19}ClN_4$	189
cyamemazine	INN	[3546-03-0]	Tercian	$C_{19}H_{21}N_3S$	190
dixyrazine		[2470-73-7]	Esucos	$C_{24}H_{33}N_3O_2S$	191
droperidol	INN, BAN, JAN, USAN	[548-73-2]	Inapsine	$C_{22}H_{22}FN_3O_2$	192
flupentixol	INN[d]	[2709-56-0]	Fluanxol	$C_{23}H_{25}F_3N_2OS$	193
flupentixol decanoate		[30909-51-4]	Fluanxol	$C_{33}H_{43}F_3N_2O_2S$	193
fluphenazine	INN, BAN	[69-23-8]		$C_{22}H_{26}F_3N_3OS$	
fluphenazine enanthate	JAN, USAN	[2746-81-8]	Prolixin	$C_{29}H_{38}F_3N_3O_2S$	194
fluphenazine decanoate	USAN	[5002-47-1]		$C_{32}H_{44}F_3N_3O_2S$	
fluphenazine hydrochloride	BAN, JAN, USAN	[146-56-5]		$C_{22}H_{28}Cl_2F_3$-N_3OS	
fluspirilene	INN, BAN, USAN	[1841-19-6]	Imap	$C_{29}H_{31}F_2N_3O$	195
haloperidol	INN, BAN, JAN, USAN	[52-86-8]	Haldol	$C_{21}H_{23}ClFNO_2$	196
haloperidol decanoate	BAN, JAN, USAN	[74050-97-8]	Haldol	$C_{31}H_{41}ClFNO_3$	196
levomepromazine	INN[e]	[60-99-1]		$C_{19}H_{24}N_2OS$	
levomepromazine hydrochloride	JAN	[4185-80-2]	Nozinan	$C_{19}H_{25}ClN_2OS$	197
levomepromazine maleate	JAN	[7104-38-3]	Nozinan	$C_{23}H_{28}N_2O_5S$	197
loxapine	INN, BAN, USAN	[1977-10-2]	Loxapac	$C_{18}H_{18}ClN_3O$	198
loxapine succinate	USAN	[27833-64-3]		$C_{22}H_{24}ClN_3O_5$	
loxapine hydrochloride		[54810-23-0]		$C_{18}H_{19}Cl_2N_3O$	
melperone	INN, BAN	[3575-80-2]	Eunerpan	$C_{16}H_{22}FNO$	199
melperone hydrochloride		[1622-79-3]		$C_{16}H_{23}ClFNO$	
mesoridazine	INN, BAN, USAN	[5588-33-0]	Serentil	$C_{21}H_{26}N_2OS_2$	200
mesoridazine besylate	USAN	[32672-69-8]	Serentil	$C_{27}H_{32}N_2O_4S_3$	200
molindone	INN, BAN	[7416-34-4]	Moban	$C_{16}H_{24}N_2O_2$	201
molindone hydrochloride	USAN	[15622-65-8]		$C_{16}H_{25}ClN_2O_2$	
mosapramine	INN[f]	[89419-40-9]	Cremin	$C_{28}H_{35}ClN_4O$	202
nemonapride	INN, JAN	[93664-94-9]	Emirace	$C_{21}H_{26}ClN_3O_2$	203

Table 5. ***Continued***

Agents	Nomen-clature[a]	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
oxypertine	INN, BAN, JAN, USAN	[153-87-7]	Forit	$C_{23}H_{29}N_3O_2$	204
perazine	JAN	[84-97-9]	Taxilan	$C_{20}H_{25}N_3S$	205
periciazine	INN[g]	[2622-26-6]	Neuleptil	$C_{21}H_{23}N_3OS$	206
perphenazine	INN, BAN, JAN, USAN	[58-39-9]	Trilafon	$C_{21}H_{26}ClN_3OS$	207
pimozide	INN, BAN, JAN, USAN	[2062-78-4]	Orap	$C_{28}H_{29}F_2N_3O$	208
pipamperone	INN, BAN, USAN[h]	[1893-33-0]	Dipiperon	$C_{21}H_{30}FN_3O_2$	209
pipamperone hydrochloride	JAN	[2448-68-2]	Dipiperon	$C_{21}H_{32}Cl_2FN_3O_2$	209
prochlorperazine	INN, BAN, JAN, USAN	[58-38-8]	Compazine	$C_{20}H_{24}ClN_3S$	210
promazine	INN, BAN	[58-40-2]	Talofen,	$C_{17}H_{20}N_2S$	211
promazine hydrochloride	USAN	[53-60-1]	Sparine	$C_{17}H_{21}ClN_2S$	211
prothipendyl	INN, BAN	[303-69-5]	Dominal	$C_{16}H_{19}N_3S$	190
risperidone	INN, BAN, USAN	[106266-06-2]	Risperdal	$C_{23}H_{27}FN_4O_2$	212
sulpiride	INN, BAN, JAN, USAN	[15676-16-1]	Dogmatil	$C_{15}H_{23}N_3O_4S$	213
sultopride	INN	[53583-79-2]	Barnetil	$C_{17}H_{26}N_2O_4S$	214
thiopropazate	INN, BAN	[84-06-0]	Dartal	$C_{23}H_{28}ClN_3O_2S$	204
thioridazine	INN, BAN, USAN	[50-52-2]	Melleril	$C_{21}H_{26}N_2S_2$	215
thioridazine hydrochloride	JAN, USAN	[130-61-0]	Melleril	$C_{21}H_{27}ClN_2S_2$	215
tiapride	INN, BAN	[51012-32-9]	Gramalil,	$C_{15}H_{24}N_2O_4S$	216
tiapride hydrochloride	BAN	[51012-33-0]	Tiapridal	$C_{15}H_{25}ClN_2O_4S$	216
timiperone	INN, JAN	[57648-21-2]	Tolopelon	$C_{22}H_{24}FN_3OS$	217
tiotixene	INN, JAN[i]	[5591-45-7]	Navane	$C_{23}H_{29}N_3O_2S_2$	218
trifluoperazine	INN, BAN	[117-89-5]	Stelazine	$C_{21}H_{24}F_3N_3S$	219
trifluoperazine hydrochloride	INN, BAN, USAN	[440-17-5]		$C_{21}H_{26}Cl_2F_3N_3S$	
triflupromazine	INN, USAN[j]	[146-54-3]	Psyquil	$C_{18}H_{19}F_3N_2S$	220
zotepine	INN, JAN	[26615-21-4]	Lodopin	$C_{18}H_{18}ClNOS$	221
zuclopenthixol	INN, BAN[k]	[53772-83-1]	Cisordinol, Sedanxol	$C_{22}H_{25}ClN_2OS$	222

[a] International nonproprietary name (INN), British approved name (BAN), Japanese accepted name (JAN), and United States adopted name (USAN).

[b] Only selected salts are included. Trade names shown can represent the base or any of the salts included in nomenclature column of the table.

[c] BAN, USAN = chlothiapine.

[d] BAN = flupenthioxal.

[e] BAN, USAN = methotrimeprazine.

[f] JAN = mosapramine hydrochloride.

[g] BAN = pericyazine; JAN = propericiazine.

[h] Also called fluoropipamide.

[i] BAN, USAN = thiothixene.

[j] BAN = fluopromazine.

[k] (Z)-isomer of clopenthiol.

32 PSYCHOPHARMACOLOGICAL AGENTS

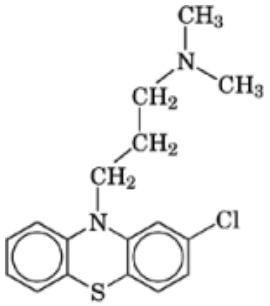
3.1. Classification of Psychoses

Schizophrenia is characterized in the DSM-IV classification system (1) by a number of symptoms of which typically two or more should be present for most of the time during a period of one month: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and/or negative symptoms such as affective flattening, alogia, and avolition. Disorders of thought processes in schizophrenics can be seen in their writing and speech, taking the form of illogical thought patterns. Schizophrenics often run together a number of logically unconnected topics and use words in a meaningless way or indeed use meaningless words. Disorders of thought, however, can also take the form of elaborate fantasies, often on profound topics and matters of principle. There may be a flattening of emotion and patients may remain impassive when confronted with situations that would normally elicit a marked response. Patients often report loss of will power and sometimes feel that they are being controlled by forces outside themselves. There are varying losses of coordination of body movements which can range from awkwardness to chaotic overactivity to catatonia. Delusions and auditory hallucinations are common.

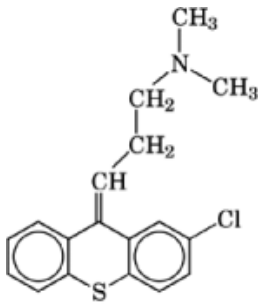
As for most psychiatric disorders, speculations concerning the pathology of the disease come from the limited understanding of the pharmacology of drugs effective in symptomatically treating the disorder. However, because the most effective antipsychotic drugs interact with numerous molecular targets, their mechanism of action in treating this disorder remains unclear.

3.2. Pharmacological Profiles of Antipsychotics

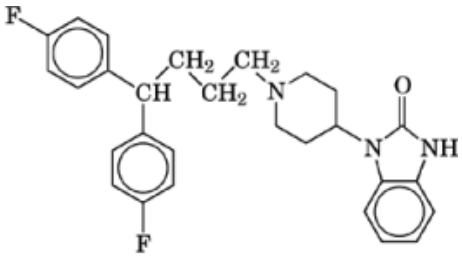
Most compounds used for antipsychotic therapy can be assigned to one of four structurally distinct groups. These are phenothiazines, eg, chlorpromazine **(56)**; thioxanthenes, eg, chlorprothixene **(57)**; diphenylbutylpiperidines, eg, pimozide **(58)**; and butyrophenones, eg, haloperidol **(59)**. Those antipsychotics most widely used clinically are included in Table 5. These compounds represent more than 97% of total units sold worldwide, but only about half of the antipsychotics clinically available. In view of the dopaminergic blocking action of compounds from these classes, some are used predominantly or even solely as antiemetics, including alizapride [59338-93-1], clebopride [55905-53-8], domperidone [57808-66-9], metoclopramide [364-62-5], oxypendyl [5585-93-3], and promethazine [60-87-7].



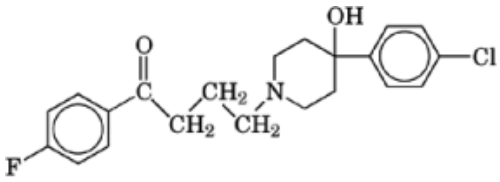
(56)



(**57**)



(**58**)

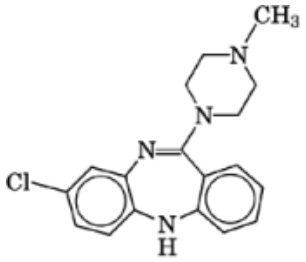


(**59**)

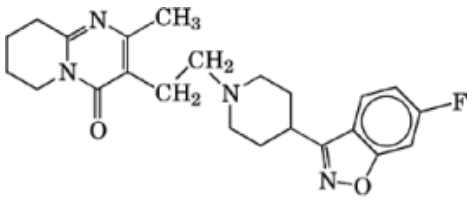
There is a good correlation between the affinity of antipsychotics for the dopamine D_2 receptor and their clinically effective dose used in the treatment of schizophrenia, suggesting the special importance of this neurotransmitter system with respect to schizophrenia (223). There are two principal dopaminergic pathways in the brain which project forward from cell bodies in the midbrain: the nigrostriatal dopaminergic pathway and the mesocorticolimbic dopaminergic pathway. It has been hypothesized that antipsychotic activity results from the blockade of dopaminergic transmission in the mesolimbic pathway, whereas blockade of dopaminergic transmission in the nigrostriatal pathway gives rise to extrapyramidal side effects such as tardive dyskinesia, akathisia, and Parkinsonian-like symptoms often associated with antipsychotic treatment (224). Therefore, antidopaminergic properties may account for both therapeutic actions and adverse effects of these drugs. However, these effects may be separable. The target of preclinical research is an antipsychotic drug that lacks extrapyramidal side effects. One such atypical antipsychotic is clozapine **(60)** which is effective in treating most of the symptoms of schizophrenia and has minimal or no concomitant extrapyramidal side effects.

Correlation between clinical effectiveness and receptor affinities, however, can be seen with other receptors in addition to the dopamine D_2 receptor. These include other dopaminergic receptors, as well as noradrenergic and serotonergic receptors. For example, most antipsychotics also have high affinity for α_1-adrenoceptors and

5-HT_{2A} receptors (225). Some antipsychotics have been shown to be selective for the α_{1B}-adrenoceptor versus the α_{1A}-adrenoceptor, for example, spiperone [749-02-0] (226) and risperidone **(61)** (227).



(60)



(61)

More interesting is the mechanism of action of atypical antipsychotics, particularly clozapine **(60)**. It is also probably the least selective antipsychotic used in the clinic, having high affinity for numerous receptors including 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7; dopamine D_1, D_2, D_3, and D_4 receptors; H_1; all five subtypes of muscarinic cholinergic receptors; and α_1-adrenoceptors. One or more of these receptors might contribute to the atypical therapeutic profile of clozapine. With the possible exception of the dopamine D_4 receptor, the high affinity of clozapine for these other sites is not shared by other atypical antipsychotics; for example, risperidone **(61)** has low affinity for the 5-HT_6 receptor and melperone [3575-80-2] has low affinity for the 5-HT_7 receptor (228). In the case of the dopamine D_4 receptor, there is also a good correlation between the affinities of most antipsychotics for the dopamine D_4 receptor and their clinically active dose. Although this may suggest that the dopamine D_4 receptor is an important receptor with respect to antipsychotic effects, at the same time it argues against the likelihood that high affinity for this receptor is solely responsible for the atypical profile of clozapine. Careful evaluation of the affinity of clozapine **(60)** for the dopamine D_2 receptor reveals that, in fact, the compound has less than one logarithmic unit of binding selectivity for the dopamine D_4 receptor versus the dopamine D_2 receptor (229, 230).

It has been suggested that high affinity for certain 5-HT receptors is a possible method for reducing extrapyramidal side effects observed with antipsychotics. Liability for extrapyramidal side effects has been hypothesized to be related to the ratio of the affinity between dopamine D_1/D_2 receptor binding sites and 5-HT_{2A} receptor binding sites (231). Risperidone **(61)** has high affinity for dopamine D_2 and 5-HT_{2A} receptors and in clinical trials has been reported to have only a weak tendency to induce extrapyramidal side effects; however, clear demonstration of its advantage in treating all the various symptoms of schizophrenia awaits further clinical results.

3.3. Future Outlook for Antipsychotics

Preclinical work is focused on the development of atypical antipsychotics having a favorable clinical profile similar to that of clozapine **(60)**. As of the mid-1990s, a wide variety of potential drug targets are being pursued (181). Compounds exhibiting high affinity binding to several receptors such as 5-HT_{2A}, dopamine D_1 and dopamine D_2 receptors, ie, risperidone-like compounds, as well as compounds that have high affinity and selectivity for only a specific receptor, eg, dopamine D_4, 5-HT_{1A}, 5-HT_{2C}, or 5-HT_6 receptors, are under consideration. In addition, the so-called σ-receptor provides an interesting drug target. It is located throughout the central nervous system as well as in peripheral tissues. Its biochemical and physiological functions are as yet poorly understood. The identification of three binding site subtypes has added to the complexity of this research area. However, because many antipsychotic agents bind to σ-sites, it has been postulated that selective σ-receptor ligands might prove useful in treating schizophrenia. It has furthermore been hypothesized that neurotensin analogues, opioid peptides, and cholecystokinin receptor agonists might exhibit antipsychotic effects.

4. Drugs for Treating Substance Use Disorders

It has been estimated that about one out of every seven adults in the United States abuses or is dependent on alcohol with an additional one out of every 20 persons abusing or dependent on other drugs (232). Certainly, the abuse and dependence on ethyl alcohol [64-17-5], nicotine [54-11-5], cocaine [50-36-2], and heroin [561-27-3] (diacetylmorphine), in particular, have produced devastating socioeconomic consequences. The similarity of psychosocial factors leading to abuse of these drugs, despite their diverse pharmacological mechanisms, suggests the predominant role played by the former in both the development and maintenance of substance abuse disorders, and consequently has resulted in an emphasis on social and behavioral treatment approaches (233). Aside from the clear therapeutic value of pharmacological treatment for both severe intoxication and acute withdrawal phenomena, protracted substance abuse and dependence may also prove amenable to therapy with pharmacologic agents.

4.1. Classification of Substance-Related Disorders

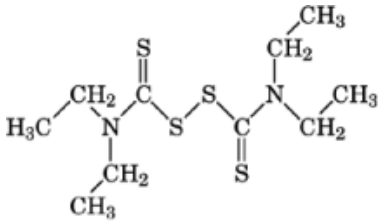
The DSM-IV classification system (1) divides substance-related disorders into two categories: (*1*) substance use disorders, ie, abuse and dependence; and (*2*) substance-induced disorders, intoxication, withdrawal, delirium, persisting dementia, persisting amnestic disorder, psychotic disorder, mood disorder, anxiety disorder, sexual dysfunction, and sleep disorder. The different classes of substances addressed herein are alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics, polysubstance, and others. On the basis of their significant socioeconomic impact, alcohol, nicotine, cocaine, and opioids have been selected for discussion herein.

4.2. Pharmacological Profiles of Agents Used to Treat Substance Use Disorders

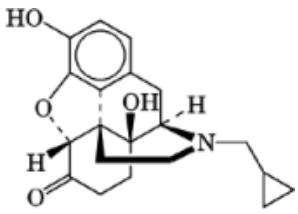
The subjective effects of drugs leading to their abuse are the result of modulation of brain neurotransmitter systems (234). Alcohol, as well as a number of other central nervous system (CNS) depressants such as benzodiazepines and barbiturates, enhances central GABAergic activity which normally serves as the main inhibitory neurotransmitter system in the brain. Nicotine exerts its effects on brain function via nicotinic acetylcholine receptors. Cocaine and other CNS stimulants facilitate the presynaptic release of catecholamines and block their reuptake by neurons. Depletion of neuronal stores of dopamine and noradrenaline has been hypothesized to underlie the depression accompanying withdrawal. Opiates act at brain receptors, eg, μ-opioid

receptors are hypothesized to be most important for the subjective effects of opioids, reduce noradrenergic tone, and their withdrawal results in rebound hyperactivity of this system in both the brain and periphery.

One approach taken to the treatment of chronic alcoholism relies on a form of aversion therapy involving prophylactic administration of inhibitors of aldehyde dehydrogenase, such as disulfiram [97-77-8] **(62)** and calcium carbimide [156-62-7], $CaCN_2$. Any consumption of alcohol then results in an accumulation of acetaldehyde yielding flushing hypotension, tachycardia, nausea, and vomiting. However, it has been reported that the efficacy of disulfiram in reducing relapse is only modest, primarily owing to noncompliance (235). More recently, the μ-opiate antagonist naltrexone [16590-41-3] **(63)** was approved in the United States for the treatment of alcohol abuse. Clinical results suggest that relapse rate in alcoholics may also be reduced by SSRIs, dopaminergic agents, lithium salts, β-adrenergic blockers, carbamazepine, and hydroxyzine.



(62)



(63)

An approved pharmacologic approach to stopping tobacco smoking, ie, nicotine dependence, involves the substitution of nicotine-containing chewing gum or a dermal patch with subsequent gradual reduction of the nicotine dose until dependence has been eliminated. The treatment of chronic CNS stimulant abuse and dependence is based primarily on the control of craving by support and minimizing contact with situations apt to trigger craving. Possible adjunctive pharmacologic treatments which hold promise include tricyclic antidepressants and carbamazepine [298-46-4].

A common strategy for treating chronic opiate addiction involves the substitution of methadone which can either be provided as maintenance therapy or tapered until abstinence is achieved. Naltrexone and buprenorphine [52485-79-7] have also been used in this manner. The α_2-adrenergic agonist clonidine [4205-90-7] provides some relief from the symptoms of opiate withdrawal, probably the result of its mimicking the inhibitory effect of opiates on the activity of *locus coeruleus* neurons.

4.3. Future Outlook for Pharmacologic Treatment of Abuse and Dependence

The importance of the psychosocial dimension in predisposing individuals toward substance use disorders and subsequently maintaining the disorder cannot be overestimated. Additionally, genetic influences have been found to exert an important influence on liability for drug abuse. A high comorbidity of psychiatric illnesses with substance use disorders further complicates therapeutic interventions in such patients (236).

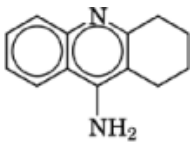
The roles of pharmacologic treatments have been mostly restricted to countering overdose and ameliorating symptoms of acute withdrawal, ie, substance-induced disorders. Effective reduction of craving for abused substances has proved difficult to achieve except through substitution strategy which may reduce some problems but fails to eliminate dependence. However, in view of the immensity of the social and medical problems, the search for pharmacological treatment remains a worthy goal. Elucidation of the neurobiological bases of reward/aversion processes, the lowest common denominator for abuse and dependence, may yield anticraving drugs and drugs effective in reducing dependence (237).

5. Cognition Enhancers

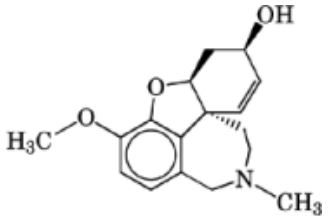
Cognitive impairment can arise through diverse pathophysiological mechanisms including, most prominently, primary degenerative dementias such as Alzheimer's disease, Parkinson's disease, and Pick's disease as well as multi-infarct dementia, cerebral vascular accidents, CNS trauma, tumors, and other causes. Until recently agents for symptomatic therapy have not received general recognition as efficacious and, although preventative measures for dementias with cardiovascular etiologies could sometimes be applied, as of the mid-1990s no drugs were approved for prevention or slowing of the progression of dementias of primary degenerative origin.

In view of the devastating socioeconomic consequences of senile dementia of Alzheimer's type (SDAT), this has received considerable attention (238), although cognitive disorders can occur throughout the life span owing to diverse etiologies. SDAT is the most common dementing disease, affecting one of every six individuals over 65 years of age. A common feature is the dysfunction or death of selective populations of neurons. For example, basal forebrain cholinergic neurons are vulnerable and their degeneration results in loss of hippocampal and cortical cholinergic function.

The acetylcholinesterase inhibitor tacrine **(64)** was approved for the treatment of mild-to-moderate SDAT in the United States in 1993 followed by several other countries. The acetylcholinesterase inhibitor galanthamine **(65)**, which has long been in clinical use in Austria for the treatment of indications such as facial neuralgia and residual poliomyelitis paralysis, has also been approved for use in



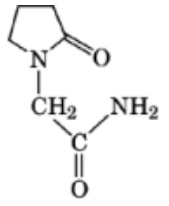
(**64**)



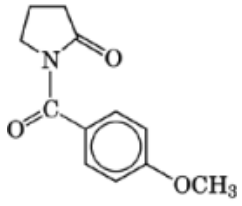
(**65**)

Alzheimer's disease in that country (239). There are a variety of other drugs marketed in one or more countries for this or related indications (240). Codergocrine mesylate, a mixture of three dihydrogenated ergot alkaloids, has been marketed worldwide since the 1950s for treating cognitive impairment or dementia.

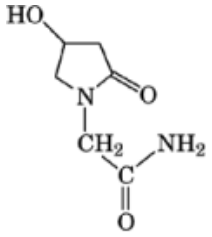
Other drugs such as meclophenoxate, bifemelane, vincamine, vinpocetine, cyclandelate, naftidrofuryl, pyritinol, idebenone, and indeloxazine are used in some countries. Piracetam **(66)** and a number of other structurally related pyrrolidinones, eg, aniracetam **(67)**, oxiracetam **(68)**, and pramiracetam **(69)** constitute the nootropic class of cognition enhancers used in treating dementia. Table 6 lists selected drugs in use as cognition enhancers (see Memory-enhancing drugs).



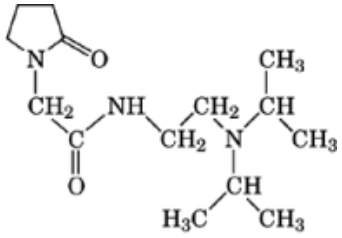
(66)



(67)



(68)



(69)

5.1. Pharmacological Profiles of Cognition Enhancers

The common denominator of most of the cognition enhancers marketed or in clinical development is the ability to reverse learning and memory deficits in animal models. However, the putative neurobiological mechanisms of action of these compounds cover a wide range of mechanisms. The so-called cholinergic hypothesis has evolved

with the accumulation of evidence that cognitive deficits associated with aging or with degenerative disorders result, at least in part, from impaired brain cholinergic function. A variety of drug development approaches focusing on cholinomimetic mechanisms have been clinically investigated.

Putative mechanism of action	Representative substances
cholinesterase inhibitors	physostigmine [57-47-6]
	E2020 [120011-70-3]
	eptastigmine [121652-76-4]
cholinomimetics	arecoline [63-75-2]
	bethanechol [590-63-6]
	AF102B [107233-08-9]
	SDZ 212-713 [123441-03-2]
acetylcholine precursors	choline [62-49-7]
	citicoline [987-78-0]
	lecithin [8002-43-5]
acetylcholine releasers	aniracetam [72432-10-1]
	acetyl-L-carnitine [5080-50-2]
	nefiracetam [77191-36-7]
	DUP996 [105431-72-9]
nicotine receptor agonists	nicotine [54-11-5]
neuropeptides	antigalanin agents
	somatostatin [51110-01-0]
	thyrotropin-releasing hormone [24305-27-9]

However, clinical results with compounds enhancing cholinergic function have not been overly convincing (272). In the case of tacrine, however, the beneficial therapeutic index was sufficient to justify regulatory approval in several countries. Psychostimulants such as pemoline, amphetamine, procaine, and methylphenidate have failed to show cognitive enhancing effects in patients with dementia, except possibly as indirect consequences of mood elevation.

Table 6. Marketed Drugs Used as Cognition Enhancers

Agent	Nomen-clature[a]	Other name(s) or salts	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
amfetamine	INN	amphetamine (BAN); amphetamine sulfate (USAN)	[300-62-9]	Benzadrine	$C_9H_{13}N$	241
aniracetam	INN, USAN		[72432-10-1]	Draganon	$C_{12}H_{13}NO_3$	242
bifemelane	INN	bifemelane hydrochloride (JAN)	[90293-01-9]	Alnert, Celeport	$C_{18}H_{23}NO$	243
cinnarizine	INN, BAN, JAN, USAN		[298-57-7]	Aplactan	$C_{26}H_{28}N_2$	244
clonidine	INN, BAN, USAN	clonidine hydrochloride (BAN, JAN, USAN)	[4205-90-7]	Catapres-TTS	$C_9H_9Cl_2N_3$	245
cyclandelate	INN, BAN, JAN		[456-59-7]	Capilan	$C_{17}H_{24}O_3$	246
ergoloid mesylate	USAN	codergocrine mesylate (BAN); dihydro-ergotoxine (JAN)	[8067-24-1]	Hydergine	[c]	247
galantamine	INN[d]		[357-70-0]	Nivalin	$C_{17}H_{21}NO_3$	248
galantamine hydrobro-mide			[1953-04-4]		$C_{17}H_{22}ClNO_3$	

Table 6. ***Continued***

Agent	Nomen-clature[a]	Other name(s) or salts	CAS Registry Number	Selected trade name(s)[b]	Empirical formula	Refs.
guanfacine	INN, BAN	guanfacine hydrochloride (JAN, USAN)	[29110-47-2]	Tenex	$C_9H_9Cl_2N_3O$	249
idebenone	INN, JAN		[58186-27-9]	Aban, Avan	$C_{19}H_{30}O_5$	250
indeloxazine	INN	indeloxazine hydrochloride (JAN, USAN)	[60929-23-9]	Alzene, Elen, Noin	$C_{14}H_{17}NO_2$	251
isoxsuprine	INN, BAN, JAN	isoxsupine hydrochloride (USAN)	[395-28-8]	Vasodilan	$C_{18}H_{23}NO_3$	252
levodopa	INN, BAN, JAN, USAN		[59-92-7]	Larodopa	$C_9H_{11}NO_4$	253
meclofen-oxate	INN, BAN	meclofenoxate hydrochloride (JAN)	[51-68-3]	Brenal, Lucidril	$C_{12}H_{16}ClNO_3$	254
methyl-phenidate	INN, BAN, JAN	methylphenidate hydrochlorde (USAN)	[113-45-1]	Ritalin	$C_{14}H_{19}NO_2$	255
naftidro-furyl	INN, BAN	nafronyl oxalate (USAN)	[31329-57-4]	Praxilene	$C_{24}H_{33}NO_3$	256
naloxone	INN, BAN, JAN	naloxone hydrochloride (USAN)	[465-65-6]	Narcan	$C_{19}H_{21}NO_4$	257
naltrexone hydro-chloride		naltrexone (INN, BAN, USAN)	[16676-29-2]	Revia, Trexan	$C_{20}H_{24}ClNO_4$	258
nicergoline	INN, BAN, JAN, USAN		[27848-84-6]	Sermion, Varson	$C_{24}H_{26}$-BrN_3O_3	259
nimodipine	INN, BAN, USAN		[66085-59-4]	Nimotop, Periplum	$C_{21}H_{26}N_2O_7$	260
oxiracetam	INN, BAN		[62613-82-5]	Neuromet	$C_6H_{10}N_2O_3$	261
papaverine hydro-chloride	JAN, USAN	papaverine (BAN)	[61-25-6]	Pavabid	$C_{20}H_{22}ClNO_4$	256
pemoline	INN, BAN, JAN, USAN		[2152-34-3]	Cylert	$C_9H_8N_2O_2$	262
pentoxi-fylline	INN, JAN, USAN	oxpentifylline (BAN)	[6493-05-6]	Trental	$C_{13}H_{18}N_4O_3$	263
piracetam	INN, BAN, USAN		[7491-74-9]	Nootropil, Diemil	$C_6H_{10}N_2O_2$	264
pramirace-tam	INN	pramiracetam hydrochloride/sulfate (USANs)	[68497-62-1]	Remen, Neupramir, Pramistar	$C_{14}H_{27}N_3O_2$	265
procaine	INN, BAN	procaine hydrochloride (JAN, USAN)	[59-46-1]	Gerovital, Novocain	$C_{13}H_{20}N_2O_2$	266
propento-fylline[e]	INN, BAN, JAN		[55242-55-2]	Hextol	$C_{15}H_{22}N_4O_3$	267
pyritinol	INN, BAN	pyrithioxine, pyrithioxine hydrochloride (JANs)	[1098-97-1]	Encephabol	$C_{16}H_{20}N_2$-O_4S_2	268
tacrine	INN, BAN	tacrine hydro-chloride (USAN)	[321-64-2]	Cognex, Tha	$C_{13}H_{14}N_2$	269
vincamine	INN, BAN		[1617-90-9]	Cetal, Devincan	$C_{21}H_{26}N_2O_3$	270
vinpocetine	INN, JAN, USAN		[42971-09-5]	Calan, Cavinton, Ceractin	$C_{22}H_{26}N_2O_2$	271

[a]International nonproprietary name (INN), British approved name (BAN), Japanese accepted name (JAN), United States adopted name (USAN).

[b]Only selected salts are included. Trade names shown can represent the base or any of the salts included in "Nomenclature".

[c] Mixture of dihydroergocornine mesylate, $C_{32}H_{45}N_5O_8S$; dihydroergocristine mesylate, $C_{36}H_{45}N_5O_8S$; and dihydro-β-ergocryptine mesylate, $C_{33}H_{47}N_5O_8S$.
[d] Also named galanthamine.
[e] Also named propentophylline.

Although of possible value in treating cerebrovascular disorders, vasodilators have not proved effective in the treatment of SDAT. Neither drugs having a primary vasodilatory effect such as papaverine, cinnarizine, cyclandelate, and isoxsuprine, nor those having less clearly defined vascular effects such as meclofenoxate, vincamine, pyritinol, and pentoxifylline were found to be consistently effective. Whereas there is little support for a role of vascular abnormalities in the pathophysiology of SDAT, there are promising clinical results on nicergoline, nimodipine, and propentofylline in treating dementia, whether by cerebrovascular or neuronal mechanisms. Although monoaminergic deficits characterize SDAT, no consistent beneficial effects were demonstrated for α_2-adrenoceptor agonists (eg, clonidine or guanfacine), SSRIs, or levodopa. Promising results have been obtained using the MAO type B inhibitor L-deprenyl, but these require further confirmation. Clinical trials of opiate antagonists (naloxone, naltrexone), neuropeptide analogues such as the somatostatin analogue seglitide [81377-02-8] and the ACTH4-9 analogue ORG 2766 [50913-82-1], as well as with prolyl-endopeptidase inhibitors and angiotensin-converting enzyme inhibitors have so far failed to convincingly demonstrate symptomatic amelioration of dementia. Despite intensive preclinical and clinical efforts, the discovery of highly efficacious drugs for the symptomatic therapy of SDAT has proved elusive. The multifaceted character of this neurodegenerative disease which affects multiple neurochemical systems distributed across different brain regions requires more study (273). Interestingly, attention deficit/hyperactivity disorder (1) has been effectively treated in some patients with amphetamine, clonidine, pemoline, and methylphenidate (274).

It has been hypothesized that treatment with neurotrophic factors might be effective in slowing the progression of degenerative diseases of the nervous system (275). Because nerve growth factor (NGF) is found in the target areas for cholinergic neuronal pathways which degenerate in SDAT and clearly prevents the degeneration of cholinergic neurons in animal models, it has been suggested that increasing the concentration of endogenous NGF or an NGF mimetic could provide beneficial clinical effects in SDAT. Another member of the neurotrophin family, brain-derived neurotrophic factor (BDNF), is widely expressed in populations of neurons in the adult mammalian brain, particularly in the hippocampus and the neocortex, and like NGF has been demonstrated to exert trophic effects on cholinergic neurons of the basal forebrain. Because neurodegeneration in Alzheimer's disease extends beyond cholinergic neurons in the basal forebrain, the potentially more widespread effects of a drug which increases the concentration of BDNF or acts as a BDNF mimetic could prove advantageous.

Alzheimer's disease is characterized by excessive deposition of β-A4 protein resulting from proteolysis of the integral membrane amyloid precursor protein (APP) and point mutations in the APP-gene are linked to some familial forms of Alzheimer's disease (276, 277). Drug discovery efforts focus on interference with the presumed pathogenic process of β-A4 deposition (leading to the formation of senile plaques) via antagonism of the toxic effects of β-A4, prevention of inflammatory processes associated with the plaques, or direct inhibition of proteases generating β-A4 from APPs. However, cognitive impairment in Alzheimer's disease, in fact, correlates more closely to the occurrence of neurofibrillary tangles composed of paired helical filaments than to β-amyloid deposits. Methods to prevent the underlying abnormal phosphorylation of tau proteins are under investigation (278). Elucidation of the strong association demonstrated between the apoE4 protein variant and occurrence of late-onset Alzheimer's disease may provide additional insights into the molecular mechanisms underlying the pathogenesis of the disease and potentially also new drug targets (279).

6. Economic Aspects

Prescription sales of psychopharmacological agents represent approximately one-tenth of the total world pharmaceutical market. Antidepressants, anxiolytics, antipsychotics, and sedative–hypnotics are mature market segments characterized by effective and safe drugs, as well as the very large presence of generic drugs. In contrast, the available drugs for treating drug abuse and dependence and those for treating cognition impairment still leave room for considerable improvement. As a whole, prescription sales of these categories of psychopharmacological agents have increased considerably in the 1990s (Table 7).

Table 7. Worldwide Prescription Drug Sales, $\$ \times 10^9$

Therapeutic class	IMS code	1984[a]	1994[a]	2000[b]
anxiolytics	N5C	1.1	2.1	2.2
sedatives–hypnotics	N5B and N1A2	0.6	1.8	2.6
antidepressants	N6A and N6C	0.7	4.0	5.8
antipsychotics	N5A	0.6	1.6	3.2
anticraving agents[c]	N7B	0.05	0.4	0.6
cognition enhancers	N6D	0.3	1.2	1.8
Total		3.35	11.1	16.2

[a] Data provided courtesy of IMS Global Services.
[b] Estimated values by extrapolation.
[c] Predominantly antismoking agents.

BIBLIOGRAPHY

"Psychopharmacological Agents" in *ECT* 1st ed., Suppl. Vol., pp. 720–743, by M. Gordon and G. E. Ullyot, Smith, Kline & French Laboratories; in *ECT* 2nd ed., Vol. 16, pp. 640–679, by M. Gordon and G. E. Ullyot, Smith, Kline & French Laboratories; in *ECT* 3rd ed., Vol. 19, pp. 342–379, by L. H. Sternbach and W. D. Horst, Hoffmann-La Roche & Co., Inc.

Cited Publications

1. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., American Psychiatric Association, Washington, D.C., 1994.
2. World Health Organization, *International Statistical Classification of Diseases and Related Health Problems (ICD-10)*, 10th Rev., World Health Organization, Geneva, Switzerland, 1992.
3. M. R. Rosekind, *J. Clin. Psychiatry* **53**, 4 (1992).
4. A. F. Schatzbert, *J. Clin. Psychiatry* **52**, 5 (1991).
5. M. H. Lader, *J. Clin. Psychiatry* **49**, 213 (1988).
6. D. V. Sheehan, J. Ballenger, and G. Jacobsen, *Arch. Gen. Psychiatry* **37**, 51 (1980).
7. D. Getova and V. Georgiev, *Acta Physiol. Pharmacol. Bulg.* **13**, 43 (1987).
8. I. Haider and I. Oswald, *Br. J. Psychiatry* **118**, 519 (1971).
9. T. D. Yih and J. M. van Rossum, *J. Pharmacol. Exp. Ther.* **203**, 184 (1977).
10. G. Wahlström, *Acta Pharmacol. Toxicol.* **35**, 131 (1974).
11. WHO Expert Committee on Drug Dependence, *World Health Organization Technical Report Series 741*, WHO, Geneva, Switzerland, 1987, 1–64.
12. T. D. Yih and J. M. van Rossum, *Xenobiotica* **6**, 355 (1976).
13. S. M. Chierichetti, G. Moise, M. Galeone, G. Fiorella, and R. Lazzari, *Int. J. Clin. Pharmacol. Ther. Toxicol.* **23**, 510 (1985).
14. W. Holtermann and W. Lochner, *Arzneim. Forsch.* **22**, 1376 (1972).

15. D. W. Barron, J. W. Dundee, W. R. Gilmore, and P. J. Howard, *Br. J. Anaesth.* **38**, 802 (1966).
16. D. D. Breimer, *Eur. J. Clin. Pharmacokinet.* **10**, 263 (1976).
17. T. Walther, F. P. Meyer, K. Puchta, and H. Walther, *Int. J. Clin. Pharmacol. Ther. Toxicol.* **21**, 306 (1983).
18. D. D. Breimer and M. A. Winten, *Eur. J. Clin. Pharmacol.* **9**, 443 (1976).
19. K. D. Wolter, *Epilepsy Res. Suppl.* **3**, 99 (1991).
20. J. Dingemanse, P. H. Hutson, M. W. Langemeijer, G. Curzon, and M. Danhof, *Neuropharmacology* **27**, 467 (1988).
21. S. Toon and M. Rowland, *J. Pharmacol. Exp. Ther.* **225**, 752 (1983).
22. M. van der Graaff, N. P. E. Vermeulen, P. Heij, J. K. Boeijinga, and D. D. Breimer, *Biopharm. Drug Dispos.* **7**, 265 (1986).
23. J. A. Vida, M. L. Hooker, C. M. Samour, and J. F. Reinhard, *J. Med. Chem.* **16**, 1378 (1973).
24. F. R. Preuss and H.-W. Kopsch, *Arzneim. Forsch.* **16**, 858 (1966).
25. Y. Le Normand and co-workers, *Br. J. Clin. Pharmacol.* **26**, 589 (1988).
26. W. D. Hooper, H. E. Kunze, and M. J. Eadie, *Ther. Drug Monit.* **3**, 39 (1981).
27. T. D. Yih and J. M. van Rossum, *J. Pharmacol. Exp. Ther.* **203**, 185 (1977).
28. J. M. Hinton, *Br. J. Pharmacol.* **20**, 319 (1963).
29. J. W. Winer, R. H. Rosenwasser, and F. Jimenez, *Neurosurgery* **29**, 739 (1991).
30. D. J. Harvey, L. Glazener, D. B. Johnson, C. M. Butler, and M. G. Horning, *Drug Metab. Dispos.* **5**, 527 (1977).
31. M. J. Painter, in R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, eds., *Antiepileptic Drugs*, 3rd ed., Raven Press, New York, 1989, 329–340.
32. M. Gamski, *Ann. Acad. Med. Gedanesis* **5**, 107 (1975).
33. C. Köppel, J. Tenczer, and K.-H. Beyer, *Arzneim. Forsch.* **35**, 1334 (1985).
34. F. G. Sulman, Y. Pfeifer, and E. Superstine, *Headache* **20**, 269 (1980).
35. O. Strubelt, *Arch. Int. Pharmacodyn. Ther.* **246**, 264 (1980).
36. A. Kales, P. Houri, E. O. Bixler, and P. Silberforb, *Clin. Pharmacol. Ther.* **20**, 541 (1976).
37. American Medical Association, *New and Nonofficial Drugs*, Lippincott, Philadelphia, Pa., 1961, p. 409.
38. E. M. Wertz and co-workers, *Am. J. Vet. Res.* **49**, 1079 (1988).
39. T. Koskela and G. Wahlström, *Acta Pharmacol. Toxicol.* **64**, 308 (1989).
40. M. M. Ghoneim, *Middle East J. Anaesthesiol.* **5**, 351 (1979).
41. M. Cathelin and G. Hosxe, *Thérapeutique* **45**, 39 (1969).
42. D. D. Breimer and A. G. de Boer, *Arzneim. Forsch.* **26**, 448 (1976).
43. W. E. Haefely, in H. Möhler and M. Da Prada, eds., *The Challenge of Neuropharmacology*, Editiones Roche, Basel, Switzerland, 1994, 15–39.
44. U.S. Pat. 4,382,938 (May 10, 1983), J. P. Kaplan and P. George (to Synthélabo).
45. Eur. Pat. 50,563 (Apr. 28, 1982), J. P. Kaplan and P. George (to Synthélabo).
46. P. George and co-workers, *Farmaco* **46**(Suppl. 1), 277 (1991).
47. G. W. Dawson, S. G. Jue, and R. N. Brogden, *Drugs* **27**, 132 (1984).
48. M. P. Fernandez-Tomé, J. A. Fuentes, R. Madronero, and J. del Rio, *Arzneim. Forsch.* **25**, 926 (1975).
49. L. M. Sonne and P. Holm, *Int. Pharmacopsychiatry* **10**, 125 (1975).
50. M. S. Langley and S. P. Clissold, *Drugs* **35**, 104 (1988).
51. R. Ferrini, G. Miragoli, and B. Taccardi, *Arzneim. Forsch.* **24**, 2029 (1974).
52. L. O. Randall, W. Schallek, G. A. Heise, E. F. Keith, and R. E. Bagdon, *J. Pharmacol. Exp. Ther.* **129**, 163 (1960).
53. B. Saletu, G. Kindshofer, P. Anderer, and J. Grunberger, *Int. J. Clin. Pharmacol. Res.* **7**, 407 (1987).
54. R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, *Drugs* **20**, 161 (1980).
55. J. E. Blum, W. Haefely, M. Jalfre, P. Polc, and K. Schärer, *Arzneim. Forsch.* **23**, 377 (1973).
56. K. D. Charalampous, W. Tooley, and C. Yates, *J. Clin. Pharmacol.* **13**, 114 (1973).
57. M. Nakanishi, T. Tsumagawa, S. Shuto, T. Kenjo, and T. Fukuda, *Arzneim. Forsch.* **22**, 1905 (1972).
58. T. Kamioka, H. Takagai, S. Kobayashi, and Y. Suzuki, *Arzneim. Forsch.* **22**, 884 (1972).
59. U. Traversa, L. De Angelis, and R. Vertua, *J. Pharm. Pharmacol.* **29**, 504 (1977).
60. J. W. Dundee and S. R. Keilty, *Int. Anesthesiol. Clin.* **7**, 91 (1969).
61. S. R. Bareggi and co-workers, *Int. J. Clin. Pharmacol. Res.* **6**, 309 (1986).
62. T. Roth, ed., *Am. J. Med.* **88**(3a), 1S–48S (1990).
63. J. P. Chambon and co-workers, *Arzneim. Forsch.* **35**, 1572 (1985).

64. T. Tsumagari and co-workers, *Arzneim. Forsch.* **28**, 1158 (1978).
65. M. Otsuka, T. Tsuchiya, and S. Kitagawa, *Arzneim. Forsch.* **25**, 755 (1975).
66. E. Geller and D. Thomson, eds., *Eur. J. Anaesthesiol.* (Suppl. 2), 1–332 (1988).
67. M. A. K. Mattila and H. M. Larni, *Drugs* **20**, 353 (1980).
68. D. J. Greenblatt, R. I. Shader, and J. Koch-Weser, *Clin. Pharmacol. Ther.* **17**, 1 (1975).
69. T. Mitsushima and S. Ueki, *Folia Pharmacologica Japonica* **74**, 959 (1978).
70. T. Sukamoto, K. Aikawa, K. Ito, and T. Nose, *Folia Pharmacologica Japonica* **76**, 447 (1980).
71. W. E. Fann, W. M. Pitts, and J. C. Wheless, *Pharmacotherapy* **2**, 72 (1982).
72. T. Kamioka, I. Nakayama, T. Hara, and H. Takagi, *Arzneim. Forsch.* **28**, 838 (1978).
73. D. M. Gallant, R. Guerrero-Figueroa, and W. C. Swanson, *Curr. Ther. Res. Clin. Exp.* **15**, 123 (1973).
74. B. G. Clark, S. G. Jue, G. W. Dawson, and A. Ward, *Drugs* **31**, 500 (1986).
75. B. Ameer and D. J. Greenblatt, *Drugs* **21**, 162 (1981).
76. K. Ohata, T. Murata, S. Kohno, and H. Sakamoto, *Pharmacometrics* **29**, 913 (1985).
77. L. O. Randall, C. L. Scheckel, and W. Pool, *Arch. Int. Pharmacodyn. Ther.* **185**, 135 (1970).
78. G. Buschmann, U. G. Kuhl, and O. Rohte, *Arzneim. Forsch.* **35**, 1643 (1985).
79. T. Kamioka, I. Nakayama, S. Akiyama, and H. Takagi, *Psychopharmacology* **52**, 17 (1977).
80. L. Pieri and co-workers, *Arzneim. Forsch.* **31**, 2180 (1981).
81. M. Otsuka, T. Tsuchiya, and S. Kitagawa, *Arzneim. Forsch.* **23**, 645 (1973).
82. L. Kangas and D. D. Breimer, *Clin. Pharmacokinet.* **6**, 346 (1981).
83. A. N. Nicholson, B. M. Stone, C. H. Clarke, and H. M. Ferres, *Br. J. Clin. Pharmacol.* **3**, 429 (1976).
84. F. J. Ayd, ed., *Int. Clin. Psychopharmacol*. **5**, 1 (1990).
85. Y. Sakai, T. Deguchi, N. Iwata, M. Mori, and Y. Nishijima, *Nippon Yakurigaku Zasshi* **66**, 706 (1970).
86. T. S. Kalinina, T. L. Garibova, and T. A. Voronina, *Behav. Pharmacol.* **5**(Suppl. 1), 112 (1994).
87. J. M. Janbroers, *Clin. Ther.* **6**, 434 (1984).
88. R. C. Robichaud, J. A. Gylys, K. L. Sledge, and I. W. Hillyard, *Arch. Int. Pharmacodyn. Ther.* **185**, 213 (1970).
89. S. I. Ankier and K. L. Goa, *Drugs* **35**, 42 (1988).
90. F. Fraschini and B. Stankov, *Pharmacol. Res.* **27**, 97 (1993).
91. P. E. Keane, J. Simiand, M. Morre, and K. Bizière, *J. Pharmacol. Exp. Ther.* **245**, 962 (1988).
92. H. L. Goldberg and R. J. Finnerty, *Am. J. Psychiatry* **136**, 196 (1979).
93. G. E. Pakes, R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, *Drugs* **22**, 81 (1981).
94. U.S. Pat. 4,316,839 (Feb. 23, 1982), M. Gerecke and co-workers (to Hoffmann-La Roche Ltd.).
95. W. Hunkeler and co-workers, *Nature* **290**, 514 (1981).
96. W. Hunkeler, *Chimia* **47**, 141 (1993).
97. L. E. Hollister, B. Müller-Oerlinghausen, K. Rickels, and R. I. Shader, *J. Clin. Psychopharmacol.* **13**(Suppl. 1) (1993).
98. K. L. Goa and A. Ward, *Drugs* **32**, 114 (1986).
99. J. Silverman and W. W. Muir, *Lab. Anim. Sci.* **43**, 210 (1993).
100. B. R. Ballinger, *Br. Med. J.* **300**, 456 (1990).
101. P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekens, and F. M. Lenaerts, *Arzneim. Forsch.* **21**, 1234 (1971).
102. F. Gross, J. Tripod, and R. Meier, *Schweiz. Med. Wochenschr.* **85**, 305 (1955).
103. M. Ferreri, E. G. Hantouche, and M. Billardon, *Encéphale* **20**, 785 (1994).
104. E. F. Domino, P. Chodoff, and G. Corssen, *Clin. Pharmacol. Ther.* **6**, 279 (1966).
105. W. Haefely, R. Schaffner, P. Polc, and L. Pieri, in F. Hoffmeister and G. Stille, eds., *Psychotropic Agents, Part II: Anxiolytics, Gerontopsychopharmacological Agents, and Psychomotor Stimulants*, Springer-Verlag, Berlin, 1981, 263–283.
106. S. S. Brown and S. Goenechea, *Clin. Pharmacol. Ther.* **14**, 314 (1973).
107. W. T. Brown, *Can. Med. Assoc. J.* **102**, 510 (1970).
108. M. S. Langley and R. C. Heel, *Drugs* **35**, 334 (1988).
109. H. D. Langtry and P. Benfield, *Drugs* **40**, 291 (1990).
110. L. Julou, J. C. Blanchard, and J. F. Dreyfus, *Pharmacol. Biochem. Behav.* **23**, 653 (1985).
111. T. G. Hales and J. J. Lambert, *Br. J. Pharmacol.* **104**, 619 (1991).

112. F. Veintemilla, F. Elinder, and P. Arhem, *Eur. J. Pharmacol.* **218**, 59 (1992).
113. L. E. Hollister, B. Müller-Oerlinghausen, K. Rickels, and R. I. Shader, *J. Clin. Psychopharmacol.* **13**(Suppl. 1), 1S (1993).
114. M. Mosconi, C. Chiamulera, and G. Recchia, *Int. J. Clin. Pharmacol. Res.* **13**, 331 (1993).
115. C. S. Dommisse and P. E. Hayes, *Clin. Pharm.* **6**, 196 (1987).
116. J. H. Boyd and M. M. Weissman, *Arch. Gen. Psychiatry* **38**, 1039 (1981).
117. C. Holden, *Science* **254**, 1450 (1991).
118. M. Roth, *Pharmacopsychiatry* **25**, 18 (1992).
119. E. Richelson, *J. Clin. Psychiatry* **55**(Suppl. A), 34 (1994).
120. R. J. Chiarello and J. O. Cole, *Arch. Gen. Psychiatry* **44**, 286 (1987).
121. A. J. Azzaro and H. E. Ward, in C. R. Gray and R. E. Stitzed, eds., *Modern Pharmacology*, Little, Brown & Co., Boston, Mass., 1994, 397–411.
122. D. L. Murphy, C. S. Aulakh, N. A. Garrick, and T. Sunderland, in H. Y. Meltzer, ed., *Psychopharmacology: The Third Generation of Progress*, Raven Press, New York, 1987, 545–552.
123. S. G. Bryant, B. G. Guernsey, and N. B. Ingrim. *Clin. Pharmacol.* **2**, 525 (1983).
124. S. Garattini and T. Mennini, *Clin. Neuropharmacol.* **12**, S13 (1989).
125. A. Coppen, K. Ghose, and A. Jorgensen, *Prog. Neuropsychopharmacol.* **3**, 191 (1979).
126. S. G. Jue, G. W. Dawson, and R. N. Brogden, *Drugs* **24**, 1 (1982).
127. F. Herr, K. Voith, and J. Jaramillo, *J. Med.* **2**, 258 (1971).
128. R. J. Milne and K. L. Goa, *Drugs* **41**, 450 (1991).
129. D. McTavish and P. Benfield, *Drugs* **39**, 136 (1990).
130. A. Martin, J. M. Masson, P. Jusseaume, M. Belonde, and C. Voisinet, *Ann. Med. Psychol.* **139**, 1023 (1981).
131. D. S. Janowsky and B. Byerley, *J. Clin. Psychiatry* **45**, 3 (1984).
132. S. G. Lancaster and J. P. Gonzalez, *Drugs* **38**, 123 (1989).
133. R. M. Pinder, R. N. Brogden, T. M. Speight, and G. S. Avery, *Drugs* **13**, 161 (1977).
134. P. E. Stokes, *Clin. Ther.* **15**, 216 (1993).
135. M. I. Wilde, G. L. Plosker, and P. Benfield, *Drugs* **46**, 895 (1993).
136. S. C. Rogers and P. M. Clay, *Br. J. Psychiatry* **127**, 599 (1975).
137. J. Rigal, *Ann. Med. Psychol.* **143**, 664 (1985).
138. M. I. Gluckman and T. Baum, *Psychopharmacologia* **15**, 169 (1969).
139. Y. Pelicier, J. C. Scotto, and Y. Girard, *Sem. Ther.* **41**, 21 (1965).
140. G. Mathe and co-workers, *Biomed. Pharmacother.* **41**, 13 (1987).
141. J. R. Davidson, E. L. Giller, S. Zisook, and J. E. Overall, *Arch. Gen. Psychiatry* **45**, 120 (1988).
142. S. G. Lancaster and J. P. Gonzalez, *Drugs* **37**, 124 (1989).
143. R. M. Pinder, R. N. Brogden, T. M. Speight, and G. Avery, *Drugs* **13**, 321 (1977).
144. P. Dick, *Encéphale* **4**, 41 (1978).
145. R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, *Drugs* **16**, 273 (1976).
146. A. Stenger, J. P. Couzinier, and M. Briley, *Psychopharmacology* **91**, 147 (1987).
147. K. Bizière, J. P. Kan, J. Souilhac, J. P. Muyard, and R. Roncucci, *Arzneim. Forsch.* **32**, 824 (1982).
148. S. L. Dickinson, *Drug News Perspect.* **4**, 197 (1991).
149. A. Filtor, D. Faulds, and K. L. Goa, *Drugs* **43**, 561 (1992).
150. A. S. Eison, M. S. Eison, J. R. Torrente, R. N. Wright, and F. D. Yocca, *Psychopharmacol. Bull.* **26**, 311 (1990).
151. J. C. Rowe, *Proc. Soc. Exp. Biol. Med.* **101**, 832 (1959).
152. C. Nordin, L. Bertilsson, and B. Siwers, *Clin. Pharmacol. Ther.* **42**, 10 (1987).
153. F. Hoffmeister, F. Wuttke, and G. Kroneberg, *Arzneim. Forsch.* **19**, 846 (1969).
154. P. C. Waldmeier, *J. Pharm. Pharmacol.* **34**, 391 (1982).
155. K. L. Dechant and S. P. Clissold, *Drugs* **41**, 225 (1991).
156. G. B. Baker, R. T. Coutts, K. F. McKenna, and R. L. Sherry-McKenna, *J. Psychiat. Neurosci.* **17**, 206 (1992).
157. M. D. Mashkovsky and N. I. Andrejeva, *Arzneim. Forsch.* **31**, 75 (1981).
158. J. M. Lwoff, C. Larousse, P. Simon, and J. R. Boissier, *Therapie* **26**, 451 (1971).
159. S. C. Risch, L. Y. Huey, and D. S. Janowsky, *J. Clin. Psychiatry* **40**, 58 (1979).
160. A. Des Lauriers, J. F. Chevalier, and G. Garreau, *Ann. Med. Psychol.* **140**, 262 (1982).

161. D. Murdoch and D. McTavish, *Drugs* **44**, 604 (1992).
162. K. Yamada and T. Furukawa, *Nippon Yakurigaku Zasshi* **97**, 31 (1991).
163. M. I. Wilde and P. Benfield, *Drugs* **49**, 411 (1995).
164. A. M. Cesura and A. Pletscher, *Prog. Drug Res.* **38**, 171 (1992).
165. M. Haria, A. Fitton, and D. McTavish, *Drugs Aging* **4**, 331 (1994).
166. M. Gastpar, *Drugs* **38**, 43 (1989).
167. S. A. Montgomery, *J. Clin. Psychiatry* **54**, 119 (1993).
168. R. M. Pinder, R. N. Brogden, T. M. Speight, and G. S. Avery, *Drugs* **13**, 401 (1977).
169. D. J. Heal and W. R. Buckett, *Int. J. Geriatr. Psychiatry* **6**, 431 (1991).
170. K. Rickels and E. Schweizer, *J. Clin. Psychiatry* **51**, 9 (1990).
171. U.S. Pat. 4,018,895 (Apr. 19, 1977), B. B. Molloy and K. K. Schmiegel (to Eli Lilly & Co.).
172. U.S. Pat. 4,626,549 (Dec. 2, 1986), B. B. Molloy and K. K. Schmiegel (to Eli Lilly & Co.).
173. D. W. Robertson, J. H. Krushinski, R. W. Fuller, and J. D. Leander, *J. Med. Chem.* **31**, 1412 (1988).
174. D. S. Risley and R. J. Bopp, *Anal. Profiles Drug Subst.* **19**, 193 (1990).
175. J. W. Jefferson and J. H. Greist, *Drugs* **6**, 448 (1994).
176. H. G. Pope, Jr., S. L. McElroy, P. E. Keck, Jr., and J. I. Hudson, *Arch. Gen. Psychiatry* **48**, 62 (1991).
177. R. M. Julien, in R. M. Julien, ed., *A Primer of Drug Action*, W. H. Freeman & Co., New York, 1995, 216–232.
178. R. M. Post, T. W. Uhde, P. P. Roy-Birne, and R. Joffe, *Psychiat. Res.* **21**, 71 (1987).
179. D. Leysen and R. M. Pinder, *Annu. Rep. Med. Chem.* **29**, 1 (1994).
180. L. Ereshefsky, T. K. Tran-Johnson, and M. D. Watanabe, *Clin. Pharm.* **9**, 682 (1990).
181. G. P. Reynolds and C. Czudek, *Adv. Pharmacol.* **32**, 461 (1995).
182. J. Schmutz and C. W. Picard, in F. Hoffmeister and G. Stille, eds., *Psychotropic Agents, Part I: Antipsychotics and Antidepressants*, Springer-Verlag, Berlin, 1980, 3–26.
183. A. Delcker, M. L. Schoon, B. Oczkowski, and H. J. Gaertner, *Pharmacopsychiatry* **23**, 125 (1990).
184. P. A. J. Janssen, C. J. E. Niemegeers, and K. H. L. Schellekens, *Arzneim. Forsch.* **15**, 104, 1196 (1965).
185. P. Benfield, A. Ward, B. G. Clark, and S. G. Jue, *Drugs* **35**, 670 (1988).
186. P. A. Dixon, E. Oforah, and R. Makanjuola, *Br. J. Clin. Pharmacol.* **14**, 273 (1982).
187. B. E. Leonard, in T. R. E. Barnes, ed., *Antipsychotic Drugs and their Side-Effects*, Academic Press, London, 1993, 3–63.
188. N. C. Moore and S. Gershon, *Clin. Neuropharmacol.* **12**, 167 (1989).
189. A. Fitton and R. C. Heel, *Drugs* **40**, 722 (1990).
190. E. F. Domino, in D. H. Efron, ed., *Psychopharmacology: A Review of Progress, 1957–1967*, U.S. Government Printing Office, Washington, D.C., 1968, 1045–1056.
191. T. V. Mikhailova, A. I. Terekhina, and A. P. Gilev, *Farmakol. Toksikol.* **32**, 28 (1969).
192. P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekens, F. J. Verbruggen, and J. M. Van Nueten, *Arzneimittel-Forschung* **13**, 205 (1963).
193. T. J. Crow and E. C. Johnstone, *Br. J. Pharmacol.* **59**, 466 (1977).
194. G. E. Hogarty and co-workers, *Arch. Gen. Psychiatry* **45**, 797 (1988).
195. N. Russell, J. Landmark, H. Merskey, and T. Turpin, *Can. J. Psychiatry* **27**, 593 (1982).
196. R. Beresford and A. Ward, *Drugs* **33**, 31 (1987).
197. S. Courvoisier, R. Ducrot, J. Fournel, and L. Julou, *C. R. Soc. Biol. (Paris)* **151**, 1378 (1957).
198. M. P. Bishop, G. M. Simpson, C. W. Dunnett, and H. Kiltie, *Psychopharmacology* **51**, 107 (1977).
199. L. Bjerkenstedt, C. Härnryd, V. Grimm, G. Gullberg, and G. Sedvall, *Arch. Psychiat. Nervenkr.* **226**, 157 (1978).
200. S. Gershon, G. Sakalis, and P. A. Bowers, *J. Clin. Psychiatry* **42**, 463 (1981).
201. J. L. Claghorn, *J. Clin. Psychiatry* **46**, 30 (1985).
202. A. Miyamoto, K. Kitawaki, K. Nagao, H. Koida, and K. Nagao, *Med. Consult. New Rem.* **28**, 183 (1991).
203. S. Usuda, N. O'uchi, K. Koshiza, F. Wanibuchi, and T. Konishi, *Jpn. Pharmacol. Ther.* **18**, 135 (1990).
204. P. A. J. Janssen and F. H. L. Awouters, in P. L. Munson, ed., *Principles of Pharmacology: Basic Concepts and Clinical Applications*, Chapman & Hall, New York, 1995, 289–308.
205. H. Hadass, H. Hippius, W. Mauruschat, B. Müller-Oerlinghausen, and L. Rosenberg, *Pharmakopsychiatrie* **7**, 17 (1974).
206. A. B. Eppel and R. Mishra, *Can. J. Psychiatry* **29**, 508 (1984).
207. L. B. Hansen, N. E. Larsen, and N. Gulmann, *Psychopharmacology* **78**, 112 (1982).

208. R. McCreadie, M. Mackie, D. Morrison, and J. Kidd, *Br. J. Psychiatry* **140**, 280 (1982).
209. P. A. Janssen and F. H. Awouters, *Arzneim. Forsch.* **44**, 269 (1994).
210. B. R. S. Nakra, A. J. Bond, and M. H. Lader, *J. Clin. Pharmacol.* **15**, 449 (1975).
211. G. Sgaragli and co-workers, *Drug. Metab. Dispos.* **14**, 263 (1986).
212. A. Claus and co-workers, *Acta Psychiatr. Scand.* **85**, 295 (1992).
213. A. J. Wagstaff, A. Fitton, and P. Benfield, *CNS Drugs* **2**, 313 (1994).
214. L. Fouks, *Actual. Psychiatr.* **11**, 54 (1981).
215. G. M. Realmuto, W. D. Erickson, A. M. Yellin, J. H. Hopwood, and L. M. Greenberg, *Am. J. Psychiatry* **141**, 440 (1984).
216. E. D. Peselow and M. Stanley, *Adv. Biochem. Psychopharmacol.* **35**, 163 (1982).
217. T. Kariya and co-workers, *J. Int. Med. Res.* **11**, 66 (1983).
218. R. Bergling, T. Mjorndal, L. Oreland, U. Rapp, and S. Wold, *J. Clin. Pharmacol.* **15**, 178 (1975).
219. A. DiMascio, L. L. Havens, and G. L. Klerman, *J. Nerv. Ment. Dis.* **136**, 168 (1963).
220. J. J. Piala, J. P. High, G. L. Hassert, J. C. Burke, and B. N. Carver, *J. Pharmacol. Exp. Ther.* **127**, 55 (1959).
221. Y. Higashi, Y. Momotani, E. Suzuki, and T. Kaku, *Pharmacopsychiatry* **20**, 8 (1987).
222. F. J. Bereen, F. B. Harte, J. Maguire, and A. N. Singh, *Pharmatherapeutica* **5**, 62 (1987).
223. P. Seeman, T. Lee, M. Chau Wong, and K. Wong, *Nature* **261**, 717 (1976).
224. F. J. White and R. Y. Wang, *Science* **221**, 1054 (1983).
225. B. M. Cohen and J. F. Lipinski, *Life Sci.* **39**, 2571 (1986).
226. A. D. Michel, D. N. Loury, and R. L. Whiting, *Br. J. Pharmacol.* **98**, 883 (1989).
227. A. J. Sleight, W. Koek, and D. C. H. Bigg, *Eur. J. Pharmacol.* **238**, 407 (1993).
228. B. L. Roth and co-workers, *J. Pharmacol. Exp. Ther.* **268**, 1403 (1994).
229. M.-B. Assie, A. J. Sleight, and W. Koek, *Eur. J. Pharmacol.* **237**, 183 (1993).
230. A. Malmberg, D. M. Jackson, A. Eriksson, and N. Mohell, *Mol. Pharmacol.* **43**, 749 (1993).
231. H. Y. Meltzer, S. Matsubara, and J. Lee, *J. Pharmacol. Exp. Ther.* **251**, 238 (1989).
232. L. N. Robins and co-workers, *Arch. Gen. Psychiatry* **41**, 949 (1984).
233. P. R. Martin, D. M. Lovinger, and G. R. Breese, in P. L. Munson, ed., *Principles of Pharmacology: Basic Concepts & Clinical Applications*, Chapman & Hall, New York, 1995, 417–452.
234. Group for the Advancement of Psychiatry Committee on Alcoholism and the Addictions, *Am. J. Psychiatry* **148**, 1291 (1991).
235. R. K. Fuller and co-workers, *JAMA* **256**, 1449 (1986).
236. D. A. Regier and co-workers, *JAMA* **264**, 2511 (1990).
237. E. J. Nestler, B. T. Hope, and K. L. Widnell, *Neuron* **11**, 995 (1993).
238. W. G. Erwin, *Clin. Pharm.* **3**, 497 (1984).
239. *SCRIP* **2028**, 27 (1995).
240. W. H. Moos, R. E. Davis, R. D. Schwarz, and E. R. Gamzu, *Med. Res. Rev.* **8**, 353 (1988).
241. H. Coper and W. M. Herrmann, *Pharmacopsychiatry* **21**, 211 (1988).
242. L. Amaducci and C. G. Gottfries, eds., *Drug Invest.* **5**(Suppl. 1) (1993).
243. S. Yamagami and co-workers, *Drugs Exp. Clin. Res.* **17**, 217 (1991).
244. A. Bernard and J. M. Goffaer, *Clin. Trials J.* **5**, 945 (1968).
245. W. McEntee and R. Mair, *Ann. Neurol.* **27**, 466 (1980).
246. G. Davies and co-workers, *Age Ageing* **6**, 156 (1977).
247. J. R. Hughes, J. G. Williams, and R. D. Currier, *J. Am. Geriatr. Soc.* **24**, 490 (1976).
248. T. Thomsen, U. Bickel, J. P. Fischer, and H. Kewitz, *Dementia* **1**, 46–51 (1990).
249. J. Schlegel, E. Mohr, J. Williams, U. Mann, M. Gearing, and T. N. Chase, *Clin. Neuropharmacol.* **12**, 124 (1989).
250. A. Nagaoka, Y. Nagai, N. Yamazaki, M. Miyamoto, and Y. Kiyota, *Drug Dev. Res.* **14**, 373 (1988).
251. M. Yamamoto and M. Shimizu, *Neuropharmacology* **26**, 761 (1987).
252. P. Cook and I. James, *N. Engl. J. Med.* **305**, 1508, 1560 (1981).
253. V. Kristensen, M. Olsen, and A. Theilgaard, *Acta Psychiatr. Scand.* **55**, 41 (1977).
254. J. R. Wittenborn, *J. Ner. Ment. Dis.* **169**, 139 (1981).
255. T. Crook, S. Ferris, G. Sathananthan, A. Raskin, and S. Gershon, *Psychopharmacology* **52**, 251 (1977).
256. J. A. Yesavage, L. Hollister, and E. Buriane, *Arch. Gen. Psychiatry* **36**, 220 (1979).

257. P. N. Tariot, T. Sunderland, H. Weingartner, D. L. Murphy, M. R. Cohen, and R. M. Cohen, *Arch. Gen. Psychiatry* **43**, 727 (1986).
258. B. T. Hyham, P. J. Eslinger, and A. R. Damasio, *J. Neurol. Neurosurg. Psychiatry* **48**, 1169 (1985).
259. B. Saletu and co-workers, *Psychopharmacology* **117**, 385 (1995).
260. T. A. Ban and co-workers, *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* **14**, 525 (1990).
261. A. Giotti, ed., *Clin. Neuropharmacol*. **9**(Suppl. 3) (1986).
262. C. Eisdorfer, J. F. Conner, and F. L. Wilkie, *J. Gerontol.* **23**, 283 (1968).
263. G. Feine-Haake, *Pharmatherapeutica* **3**, 4651 (1983).
264. M. W. Vernon and E. M. Sorkin, *Drugs Aging* **1**, 17 (1991).
265. R. J. Branconnier, J. O. Cole, E. C. Dessain, K. Spera, S. Ghazvinian, and D. DeVit, *Psychopharmacol. Bull.* **19**, 726 (1983).
266. P. Goodnick and S. Gershon, *J. Clin. Psychiatry* **45**, 196 (1984).
267. H.-J. Möller, I. Mauer, and B. Saletu, *Pharmacopsychiatry* **27**, 159 (1994).
268. K. J. Martin, *J. Int. Med. Res.* **11**, 55 (1983).
269. K. L. Davis and co-workers, *N. Eng. J. Med.* **327**, 1253 (1992).
270. S. Hagstadius, L. Gustafson, and J. Risberg, *Psychopharmacology* **83**, 321 (1984).
271. D. M. Coleston and I. Hindmarch, *Drug Dev. Res.* **14**, 191 (1988).
272. B. E. Leonard, *Med. Sci. Res.* **18**, 663 (1990).
273. B. W. Volger, *Clin. Pharm.* **10**, 447 (1991).
274. M. R. Jacobs and K. O'B. Fehr, *Addiction Research Foundation's Drugs and Drug Abuse*, 2nd ed., Addiction Research Foundation, Toronto, Canada, 1987, 3–640.
275. P. J. Isackson and K. D. Murray, *Drug News Perspect.* **7**, 585 (1994).
276. M.-C. Chartier-Harlin and co-workers, *Nature* **353**, 844 (1991).
277. S. Gandy and P. Greengard, *Int. Rev. Neurobiol.* **36**, 29 (1994).
278. K. S. Kosik, *Trends Neurosci.* **14**, 218 (1991).
279. E. H. Corder and co-workers, *Science* **261**, 921 (1993).

J. R. MARTIN
F. Hoffmann-La Roche, Ltd.
T. GODEL
F. Hoffmann-La Roche, Ltd.
W. HUNKELER
F. Hoffmann-La Roche, Ltd.
F. JENCK
F. Hoffmann-La Roche, Ltd.
J.-L. MOREAU
F. Hoffmann-La Roche, Ltd.
A. J. SLEIGHT
F. Hoffmann-La Roche, Ltd.
U. WIDMER
F. Hoffmann-La Roche, Ltd.

Related Articles

Hypnotics, sedatives, anticonvulsants, and anxiolytics; Neuroregulators; Histamines and histamine antagonists; Pharmaceuticals