Chapter 15

Sedative-Hypnotics

Nader H. Moniri

Drugs Covered in This Chapter

Barbiturates

- Amobarbital
- Butabarbita
- Pentobarbital
- Phenobarbital
- Secobarbital
- Thiamylal
- Thiobarbital

Benzodiazepine sedative-hypnotics

- Estazolam
- Flurazepam
- Quazepam
- Temazepam
- Triazolam

Histamine H_1 receptor antagonists

- Diphenhydramine
- Doxepin
- Doxylamine

Melatonin receptor agonists

- Ramelteon

Nonbenzodiazepine sedative-hypnotics

- Eszopiclone
- Zaleplon
- Zolpidem

Abbreviations

AA-NAT, arylalkylamine *N*-acetyltransferase
AMP, adenosine monophosphate
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
APR, antiplanar region
ARAS, ascending reticular activating system
BZ, benzodiazepine
CNS, central nervous system
EEG, electroencephalography
ERR, electron-rich region
FDA, U.S. Food and Drug Administration
FRAR, freely rotating aromatic ring region
$GABA_A$, γ-aminobutyric acid A receptors
GPCR, G protein–coupled receptor
HIOMT, hydroxyindole-*O*-methyltransferase
MT, melatonin
NPS, neuropeptide S
PAR, planar aromatic region
PKA, protein kinase A
REM, rapid eye movement
SAR, structure–activity relationship
SCN, suprachiasmatic nucleus
TMH, transmembrane helix
TMN, tuberomammillary nucleus

SCENARIO

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WK, a 78-year-old white woman, presents to the ambulatory care clinic for a medication therapy management (MTM) consult before her appointment for a routine examination with her primary care provider. WK is accompanied by her daughter, with whom she lives. WK's medical problems (and medications) are type 2 diabetes (glipizide 5 mg po QD), hypertension (verapamil SR 180 mg po QD), osteoporosis (alendronate 70 mg po once weekly, calcium carbonate 600 mg/vitamin D 200 iu po BID), and insomnia (zolpidem 5 mg po Q HS). WK's problems have been controlled, but at today's visit, an 8-lb weight gain in 6 months is noted. Her hemoglobin A_{1C} level is now 7.6% but it had been stable at 6.8%, and her blood pressure is 126/78 mm Hg. The daughter reports that her mom has begun to wander through the house at night and has been found on several occasions eating warmed-up leftovers at 2 AM. The daughter also reports that WK has begun to experience memory loss. WK denies these behaviors and reports that she falls asleep just fine, but she is not sleeping well during the night. WK is also concerned about her recent weight gain and she confides that, as a result of her visit to the dermatologist last month, she was prescribed a new medicine, itraconazole capsules, for the newly diagnosed fungal infection in the fingernails on her right hand.

(The reader is directed to the clinical solution and chemical analysis of this case at the end of the chapter).

INTRODUCTION

The general objective of this chapter is to provide the reader with an in-depth understanding of the molecular and chemical basis of sedative-hypnotic drug action. The reader is first introduced to neuronal regulation of the sleep/wake cycle and the effects on regulating the stages of sleep. Emphasis is placed on introducing the targets of sedative-hypnotic agents, particularly γ-aminobutyric acid A receptors ($GABA_A$), melatonin (MT) MT1/MT2 receptors, and histamine H_1 receptors. Specific agents that modulate the functions of these receptors to promote sleep will be discussed from the perspectives of structure–activity relationships, as well as physiochemical and pharmacokinetic properties that affect their activity.

NEUROBIOLOGY OF SLEEP

Sleep is a reversible process that is typified by sensory and motor inactivity as well as reduced cortical responses to external stimuli. This process is distinct from complete states of unconsciousness (e.g., coma), in which decreased cortical activity is unresponsive to all external stimuli. In human physiology, sleep/wake cycles are regulated to a large degree by endogenous circadian rhythms as well as homeostatic mechanisms, which in turn are governed by a myriad of neuronal pathways. Critical experiments performed in felines in the late 1940s demonstrated that impairment of the reticular formation within the brainstem triggered behavioral and electroencephalographic (EEG) activity consistent with coma-like states, suggesting that this area of the brain was involved in regulating sleep and wakefulness (1). This was contrary to observations that showed that felines with lesions of ascending sensory neurons distal to the reticular formation displayed no impairment to wakefulness or sleep, indicating that sleep/wake regulation by the reticular formation was independent of sensory neurons that *leave* it (2). Further experiments showed that the reticular formation contained a high density of afferent input and that direct stimulation of the reticular formation facilitated wakefulness (3). Taken together, these key observations suggested that sleep and wakefulness were likely controlled by factors within the reticular formation and that this structure behaves as a relay center that transmits afferent input to the cortex. These and other pioneering studies led to the ascending reticular activating system (ARAS) hypothesis of sleep/wake regulation and subsequent identification of ARAS function as being critical in modification of sleep/wake transitions. Many decades of ensuing research on sleep/wake responses of the ARAS have revealed that projections to and from various nuclei within the brainstem can modulate ARAS activity to facilitate wakefulness and sleep. These include serotonergic neurons of the raphe nucleus within the reticular formation itself; cholinergic neurons of the pedunculopontine tegmentum and noradrenergic neurons of the locus coeruleus, within the pons; as well as dopaminergic neurons of the substantia nigra and ventral tegmental areas of the midbrain. These structures themselves are regulated in a highly orchestrated manner primarily by the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA to regulate their respective activities.

In addition to the cell structures that make up the brainstem ARAS, there are additional populations of highly specialized cells that can modulate sleep/wakefulness either independently or in concert with cells of the ARAS. For example, stimulation of the tuberomammillary nucleus (TMN) within the posterior hypothalamus facilitates wakefulness and arousal, and these cells are predominantly active only during wakeful periods (4). TMN-mediated regulation of wakefulness

is dependent on histaminergic neurons that densely project into the cortex as well as other wake-promoting structures within the brainstem (5). The firing rate of these cortical-projecting histaminergic TMN neurons decreases upon sleep and increases upon arousal, whereas lesioning of histaminergic neurons within the TMN promotes sleep (6–8). Biochemically, the release of histamine from these neurons is increased upon and during wakefulness and is under the control of glutaminergic-stimulatory and GABAergic-inhibitory circuits (9,10). Studies with histamine receptor knockout mice and in vivo pharmacologic studies have established that the TMN effects of histamine on wakefulness and sleep are mediated primarily by histamine H_1 receptors.

Whereas the posterior-hypothalamic TMN is involved in regulating arousal, the anterior-hypothalamus, specifically the suprachiasmatic nucleus (SCN), is involved in induction of sleep. This has been demonstrated by studies that show that lesions to the posterior hypothalamus (e.g., TMN) induce sleepfulness, whereas lesions of the anterior hypothalamus are associated with wakefulness (11). Decades of further work have established that the SCN is critical for the maintenance of circadian rhythms, in essence behaving as the brain's endogenous master clock, thereby regulating sleep/wake cycles and synchronizing circadian phase timings with other brain structures. Importantly, the SCN receives visual input from the retina via the retinohypothalamic tract, and this key connection serves to synchronize circadian rhythms to daylight (12). The firing rate of SCN neurons is strongly correlated with day/night cycles, which serve to establish an approximate 24-hour circadian rhythm. Although the SCN is largely under the control of glutaminergic and GABAergic neurons, which originate in the preoptic nucleus, it also works in concert with the pineal gland to regulate circadian rhythms (13). As such, inhibitory GABAergic outflow from SCN neurons to the pineal gland is enhanced during the daylight hours and declines proportionally to decreases in daylight. Light-sensitive neurons from the SCN project to the hypothalamic paraventricular nuclei and through the lateral horn of the spinal cord primarily by way of vasopressin and GABAergic neurons. The signal is then relayed to the pineal gland through noradrenergic ganglionic sympathetic fibers, which directly innervate the pineal gland. Hence, during periods of light, GABA output is elevated, which inhibits the release of norepinephrine at the pineal gland. On the contrary, during periods of darkness, the inhibitory GABAergic outflow from the SCN is reduced, resulting in increased levels of norepinephrine released at the level of the pineal gland (12). Here, norepinephrine acts primarily through pineal β_1- and α_{1B}-adrenergic receptors to stimulate a rapid and profound (~10-fold) synthesis and release of melatonin, another key regulator of circadian rhythms and the sleep/wake cycle, into the bloodstream (14).

The synthesis of melatonin occurs within the pineal gland, where the amino acid L-tryptophan is converted to serotonin, which is subsequently acetylated to yield *N*-acetylserotonin by the enzyme arylalkylamine *N*-acetyltransferase (AA-NAT). *N*-acetylserotonin is converted to melatonin by the

CLINICAL SIGNIFICANCE

Medications from several classes are useful pharmacotherapeutic agents for managing insomnia. The benzodiazepines are safe and effective and are the most commonly prescribed sedative-hypnotic agents. Within the class of benzodiazepines, those with shorter elimination half-lives, such as the triazolobenzodiazepines triazolam and estazolam, provide improved sleep patterns and minimal daytime sedation. Relative duration of action, as well as sedative-hypnotic potency and risk of residual morning depressant effects, can be readily assessed from an evaluation of benzodiazepine structure. The nonbenzodiazepine $GABA_A$ agonists of zolpidem, zaleplon, and eszopiclone have comparable efficacy to the benzodiazepines in improving sleep patterns and can be selectively used to reduce sleep latency, nighttime awakenings, and/or total sleep time. The melatonin receptor agonist ramelteon is a newer alternative as a sedative-hypnotic agent. The antihistamine H_1-receptor antagonists diphenhydramine and doxylamine, members of the highly sedative aminoalkylether class of antihistamines, as well as the antidepressants trazodone and doxepin (a member of the tertiary tricyclics well known for sedative side effects) are useful as sedative-hypnotic agents, but selection of these should be based on the side effect profile of the individual agent. Barbiturates are well established as effective sedative-hypnotic agents and their well-defined structure-activity relationships can help guide clinicians in drug product selection when they are truly indicated; however, their associated toxicities of central nervous system depression, physical dependence, and tolerance as well as their activity as potent hepatic enzyme inducers have limited their use as sedative-hypnotic agents. Identifying the chemical classes and their associated physical chemical properties and metabolic fates will greatly facilitate the understanding and utilization of these useful therapeutic agents.

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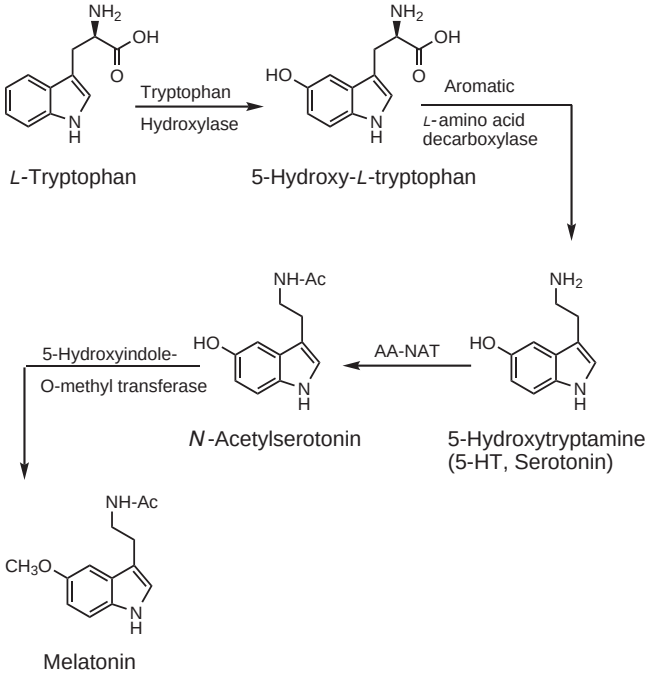


FIGURE 15.1 Biosynthesis of melatonin.

enzyme 5-hydroxyindole-*O*-methyltransferase (HIOMT) (Fig. 15.1). The activity of AA-NAT is greatly influenced by β_1-adrenergic receptors, which are activated upon the release of norepinephrine via the SCN circuit described earlier. β_1-receptor–mediated increases in intracellular cyclic adenosine monophosphate (AMP) stimulate AA-NAT expression and also increase protein kinase A (PKA)–mediated phosphorylation of AA-NAT, which stabilizes and activates the enzyme (15). The rhythm of AA-NAT activity is thus correspondingly coupled to light exposure because increases in light lead to decreases in AA-NAT activity. Activity of AA-NAT can also be effectively abolished by lesions of the SCN, further demonstrating that melatonin synthesis is dependent on retinohypothalamic input (16). Once synthesized, melatonin diffuses into capillary blood vessels and rapidly reaches all tissues of the body, where it can agonize its cognate G protein–coupled receptors (GPCRs), MT1R and MT2R, leading to various physiologic responses. With specific regard to sleep, melatonin has profound effects in the SCN, where it agonizes MT1R to mediate the acute inhibition of SCN neurons, thereby promoting sleep. Additionally, agonism of MT2R in the SCN is associated with the phase-shifting effects on circadian rhythms.

HUMAN SLEEP CYCLES

EEG has afforded researchers the ability to assess the electrical activity of the brain during the course of sleep, and these findings have revealed the presence of distinct EEG activity that correlates to five stages of sleep. These stages, which cycle throughout the night, include four non–rapid eye movement (REM) stages, often referred to as "quiet sleep," as well a single stage of REM sleep, referred to as "active sleep." Non-REM sleep stages correlate to periods of low metabolic rate and low neuronal activity; hence, brain activity and EEG events are "quiet." In non-REM sleep, heart rate and blood pressure are also reduced due to an increase in parasympathetic nervous system activity coupled with a decrease in sympathetic activity. As a result of these autonomic reflexes, non-REM sleep also causes pupillary constriction, which diminishes the amount of light that is allowed to enter the retina (17). The initial period of sleep is stage 1, which lasts only a brief period of time (5 to 15 minutes) and represents the period of transitioning from wakefulness to sleep. Although EEG activity in awake humans mainly consists of high-frequency (15 to 25 Hz) alpha-wave events, the progression to stage 1 sleep results in the emergence of slower theta waves with lower frequency (4 to 10 Hz) as the individual progresses to the light or drowsy sleep characterized by stage 1. In stage 2 sleep, which often lasts 15 to 20 minutes, background theta waves continue but are periodically interrupted by characteristic sleep spindles, which are short bursts of higher frequency (12 to 15 Hz) EEG events. Stage 2 of the sleep cycle is still considered a light sleep; however, skeletal muscle activity is decreased in this stage compared to the transitionary stage 1. Stages 3 and 4, often referred to as slow-wave sleep, are characterized by appearance of higher amplitude, slower frequency (0.5 to 4 Hz) delta waves, which occur less often in stage 3 and more often in stage 4. Both of these stages represent deep sleep because the characteristic delta activity is least similar to arousal-state alpha activity. If awakened in this stage of sleep, an individual will likely be confused and disoriented (18).

The fifth stage of sleep is referred to as REM sleep and is characterized by increases in eye movement, respiration rate, and brain activity. Electroencephalographic changes in REM sleep include high-voltage firing spikes, which seem to originate in the pons, lateral geniculate nucleus, and occipital cortex, and these spikes are correlated with bursts of rapid eye movements associated with this stage of sleep (19). The increased brain activity in REM sleep is consistent with an increase in dreaming and an increase in metabolic rate, thus the naming convention "active sleep"; yet, it is inversely proportional to skeletal muscle tonicity, which effectively paralyzes skeletal movements.

The sleep stages are normally cycled every 90 to 100 minutes throughout the night, and it is important to note that sleep does not necessarily advance sequentially through the five stages. Healthy adults typically enter sleep through a progression through the stages, with the first REM stage occurring after 75 to 90 minutes of non-REM sleep and a typical return to stage 2 or 3 sleep thereafter. As sleep progresses over the course of a night, the amount of time spent in REM sleep increases such that over a typical 8-hour sleep cycle, approximately 55% to 60% of sleep time is spent in stages 1 and 2 (light sleep), 20% in stages 3 and 4 (deep sleep), and 20% to 25% in stage 5 (REM sleep).

PHARMACOLOGIC TARGETS OF SEDATIVE-HYPNOTIC AGENTS

As described earlier in the brief introduction, there are many physiologic and biochemical factors that can influence the various stages of sleep, and as such, numerous targets for pharmacologic intervention have arisen. In fact, nearly every neurotransmitter system in the mammalian brain, including the adenosinergic, serotonergic, dopaminergic, adrenergic, histaminergic, and cholinergic systems, have at one time or another been associated with induction of sleep or wakefulness. Despite this wide breadth of potential biochemical targets, the development of sedative-hypnotic agents has primarily focused on 1) agents that cause CNS depression via agonism of $GABA_A$ receptors, and 2) agents that modulate hypothalamic histamine or melatonin circadian systems that, as described earlier, regulate sleep and arousal. This chapter will focus on structure–activity relationships (SARs) and pharmacodynamics of these agents, including barbiturates, benzodiazepines, nonbenzodiazepine $GABA_A$ agonists, melatonin receptor agonists and histamine H_1 receptor antagonists. Development of agents that modulate the activity of novel protein targets such as orexin and neuropeptide S receptors will also be discussed towards the end of the chapter.

$GABA_A$ Receptors

GABA is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS) and is critical in balancing neuronal excitation. GABA is widely distributed throughout the CNS and can be in found at concentrations up to 1,000-fold (high μmol/L to low mmol/L) greater than that of monoaminergic neurotransmitters in various CNS nuclei. GABA-induced physiologic functions are mediated by at least two distinct classes of membrane-bound receptors, ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. $GABA_B$ receptors belong to the second messenger–linked GPCR superfamily and share homology with metabotropic glutamate receptors. Meanwhile, $GABA_A$ receptors are ligand-gated ion channels that modulate conductance of chloride ions through the cell membrane upon binding of GABA. The activation of $GABA_A$ receptors on excitable neurons leads to membrane hyperpolarization, which facilitates an increase in the firing threshold potential and consequently reduces the likelihood of generating an action potential. Hence, agonism of GABA receptors leads to neuronal inhibition and CNS depression, and not surprisingly, $GABA_A$ receptors are important targets for treatment of a variety of CNS disorders in which CNS depression provides a therapeutic benefit, including anxiety (see Chapter 14), anesthesia (see Chapter 16), convulsions and seizures (see Chapter 17), and sleep disorders. In this regard, drugs that increase $GABA_A$-mediated chloride flux (e.g., $GABA_A$ agonists) provide anxiolytic, anesthetic, anticonvulsant, and sedative-hypnotic activity, whereas agents that block the chloride channel (e.g., picrotoxin) can lead to convulsions and a heightened state of arousal.

The $GABA_A$ receptor-channel complex is related to the nicotinic acetylcholine receptor superfamily, which also includes the strychnine-sensitive glycine receptors and serotonin $5\text{-}HT_3$ receptors. In the human brain, $GABA_A$ complexes are formed by oligomerization of individual subunits that produce heteropentomeric complexes consisting of α, β, γ, δ, ε, or ρ subunits, which assemble a ligand-gated channel with a central pore that allows for the conductance of chloride (Fig. 15.2) (20). Moreover, the α, β, and γ subunits of $GABA_A$ receptors are expressed as distinct alternatively spliced variants (e.g., $\alpha_{[1\text{-}6]}$, $\beta_{[1\text{-}3]}$, $\gamma_{[1\text{-}3]}$). Functional channels typically require multiple α and β subunits in combination with another subunit, allowing for tremendous diversity in the makeup of the channels (Fig. 15.2). The distribution of various $GABA_A$ receptors varies according to the subtype combinations. The $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, and $\alpha_3\beta_3\gamma_2$ subtypes are the most abundant receptors, accounting for nearly 80% of $GABA_A$ receptors in the mammalian brain (20). The α_1 subunit is the most widely expressed, whereas α_4, α_5, and α_6 subunits are restricted to localized neuronal populations (20). Two distinct GABA binding sites are formed at the two α and β subunit interfaces, whereas the binding sites for GABA-modulating drugs such as barbiturates and benzodiazepines are at allosteric sites (Fig. 15.2). Upon binding of barbiturates or benzodiazepines to their respective allosteric sites on the $GABA_A$ receptor, alterations in the conductance of Cl^- occur, as described for each class of agent in the following sections.

Barbiturates

Barbiturates are potent CNS depressants with sedative-hypnotic, anesthetic, and anticonvulsant activity and were widely considered sedative-hypnotic agents of choice until the marketing of benzodiazepines in the late 1960s. Barbiturates played a crucial role in our understanding of $GABA_A$ receptor function, and although there are special instances that call for barbiturate use, they have largely been replaced as sedative-hypnotic agents by other agents due to safety concerns, which include tolerance, dependence, potential for abuse, and a relatively low toxicity threshold that can lead to overdosage and poisoning. Currently, there are five barbiturates approved by

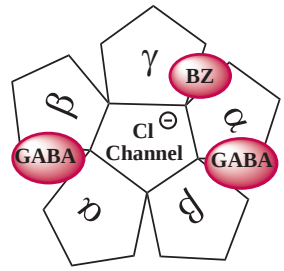


FIGURE 15.2 The pentameric assembly of $GABA_A$ receptors, whose monomers assemble to form the chloride channel at the center. The distinct GABA and benzodiazepine binding sites of this αβγ-type receptor are noted.

the U.S. Food and Drug Administration (FDA) for use as sedative-hypnotics: amobarbital, butabarbital, pentobarbital, phenobarbital, and secobarbital.

Barbiturate Mechanism of Action Upon binding of GABA to the receptor, the chloride ion (Cl^-) conductance channel opens in bursts of approximately 1 millisecond, 5 millisecond, and 10 millisecond of duration, followed by brief periods of closure. Channel opening increases in frequency and duration upon increases in GABA concentrations. Binding of barbiturates to their $GABA_A$ binding site causes an increase in the binding of GABA to the receptor, facilitating an enhancement of the actions of GABA and leading to prolongation of the longest-duration open state (21). Although the exact site of barbiturate binding remains elusive, it is known that this site is distinct from both the GABA and benzodiazepine (BZ) sites and that the barbiturate site likely does not require specific subunits, unlike the BZ site (see later discussion). Higher therapeutic concentrations of barbiturates can also enhance binding of benzodiazepines, whereas supratherapeutic concentrations of barbiturates can cause opening of the channel independently of GABA, although the clinical importance of this response has not been widely studied (22). Notably, in addition to their augmentation of $GABA_A$ responses, the physiologic effects of higher concentrations of barbiturates can also be mediated by kainite-sensitive α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptors, as well as voltage-gated Na^+ and Ca^{2+} channels.

Pharmacologic Effects of Barbiturates Barbiturates act as reversible inhibitors of virtually all excitable neurons and can produce dose-dependent CNS depression, which ranges in effect from weak sedation to general anesthesia. With regard to their effects on sleep, barbiturates significantly decrease the time it takes to fall asleep (sleep latency), increase the total time of sleep, and also decrease occurrences of nighttime awakenings. As a consequence of these effects, barbiturates significantly impair psychomotor abilities and also decrease memory and cognitive performance. Additionally, barbiturates can cause physical dependence, and sudden withdrawal of these agents can lead to serious neuropsychiatric symptoms and convulsions of excitable tissue, which can facilitate seizures and respiratory spasms. Long-term use of barbiturates has also been shown to lead to tolerance, in which higher doses of the agent are needed to achieve the same therapeutic endpoints (e.g., sleep). Because these agents have relatively narrow safety margins, higher doses that result as a consequence of tolerance can lead to toxicity. Due to these concerns, the use of barbiturates in treatment of insomnia has been virtually discontinued, and when these agents are used for treatment of insomnia, they are used in special cases and/or restricted to only short-term use. Other, older barbiturate-like drugs (e.g., chloral hydrate, glutethimide, and ethylchlorvynol) also act on the $GABA_A$ receptor to produce sedative-hypnotic effects but have fallen out of favor due to numerous untoward effects. These agents have been reviewed in previous editions of this text.

Structure–Activity Relationships of Barbiturates Barbiturates are derivatives of a cyclized ureide of malonic acid, commonly referred to as barbituric acid (2,4,6-trioxyhexahydropyrimidine) (Fig. 15.3), which is itself devoid of sedative-hypnotic, anxiolytic, and anticonvulsant activity. As shown in Figure 15.3, barbituric acid can undergo pH-dependent keto-enol tautomerization through transfer of either imino hydrogen or methylene hydrogen to a keto oxygen. This tautomerization is based on a fairly acidic carbon ($pK_a \sim 4$) at the 2-position, which can be stabilized in either molecular form based on the acidity of the solution. Empirical and computational studies have demonstrated that the tri-keto form is the most stable in aqueous solutions, whereas the 4,6-dialcohol tautomeric forms are the least stable (23,24). Although barbituric acid itself lacks pharmacologic activity, addition of 5,5-disubstituents to the barbituric backbone yields compounds with potent sedative-hypnotic, anxiolytic, and anticonvulsant activity. Termed *barbiturates*, the 5,5-disubstituted barbituric acids all possess a high degree of lipophilicity and, as weak acids, can be easily converted to sodium salts by treatment with sodium hydroxide.

Although thousands of barbiturate-like compounds have been synthesized, the 5,5-disubstituted barbituric acid backbone is the primary pharmacophore required for sedative-hypnotic activity, and efforts to further derivatize this backbone lead to a general loss in activity. These efforts show that esterification of either of the 1,3-diazine nitrogens decreases hypnotic activity. Although substitution of these nitrogens with aliphatic carbons retained anticonvulsant effects, it led to only weak hypnotic activity for *N*-methylated substituents, and this activity was lost upon increases in chain length or bulk (25,26). Likewise, esterification of the 5-position substituents (e.g., 5-phenyl, 5-methylester) yielded agents with analgesic activity but only weak hypnotic effects (27). Although early work on barbiturate derivatization demonstrated the importance of the 5-position substitutions on CNS depressant activity, the inclusion of polar functional groups at the 5-position

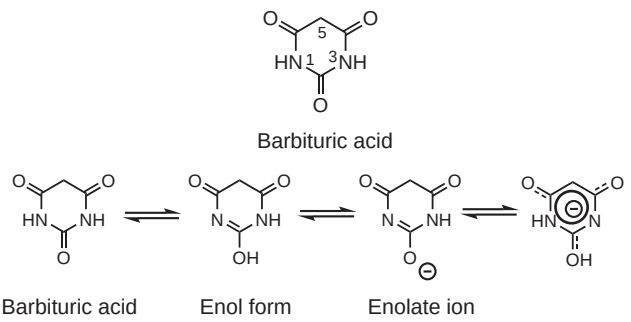


FIGURE 15.3 The structure of barbituric acid (top) and tautomerization of barbituric acid.

resulted in compounds that were fully devoid of sedative-hypnotic or anticonvulsant activity (28).

There are currently five barbiturates approved by the FDA for short-term sedative-hypnotic use and treatment of insomnia (Fig. 15.4). Structurally, pharmacologic activity is imparted to all five compounds due to the lipophilic di-substitutions at the 5-position (e.g., R_1 and R_2; Table 15.1). With the exception of secobarbital, which contains an allylic group at R_1, the remaining agents contain an ethyl substitution at this position (Fig. 15.4). Differences in these sedative-hypnotic barbiturates lie predominately at the R_2 position, where substitutions can affect the potency, rate of onset, and duration of action of the various congeners. The activity of these agents is strongly influenced by the lipophilicity of both substituents at the 5-position. As the number of carbon atoms at the R_2 position increases, the lipophilicity of the barbiturate will also increase such that comparative predictions on activity and time to onset can be made. For example, pentobarbital is more potent and has faster onset compared to butabarbital, which contains one less methylene group and is thus less lipophilic (Fig. 15.4, Table 15.1). Although the lipophilicity of the molecule greatly influences its ability to cross the blood–brain barrier, leading to potency and affecting the time of onset (see later discussion), too high a degree of lipophilicity will offset the required hydrophilicity that is necessary for dissolution and solubility of the compound in aqueous fluids. Hence, a limit to lipophilicity is reached and pharmacologic activity will begin to decrease if this threshold is surpassed.

The first commercially marketed barbiturate, barbital, contained identical 5,5-diethyl substituents, and as such, a plane of symmetry. However, many clinically useful barbiturates contain distinct 5,5-disubstitutions and substituted nitrogens, which form an asymmetric chiral center at the C-5 carbon and/or within one of the 5-position alkyl chains. Although barbiturates are dispensed as racemic mixtures, *L*-stereoisomers typically have twice the potency of the respective *D*-stereoisomers, consistent with observations that demonstrate stereoselectivity of $GABA_A$ receptors.

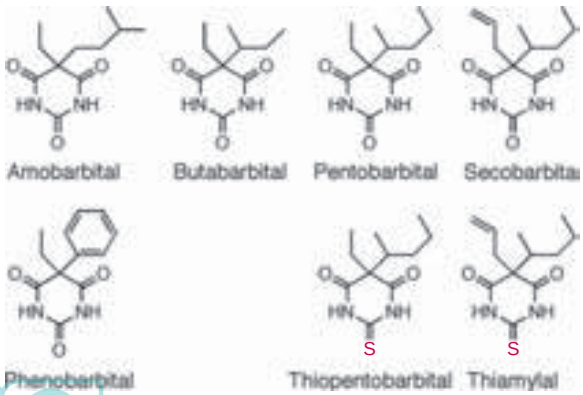


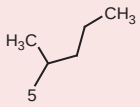
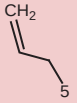
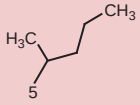
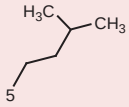
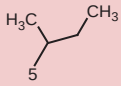
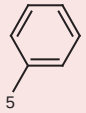
FIGURE 15.4 The barbiturates that are indicated for sedative-hypnotic use and the thiobarbiturates underneath their respective oxybarbiturate congeners.

A final note regarding the SAR of barbiturates is more critical in the role of this class as anesthetic agents and as such is only briefly discussed here. Specifically, modification of the 2-position oxygen of the barbiturate backbone with the larger sulfur atom yields thiobarbiturate derivatives with increased lipophilicity, faster time of onset, and shorter duration of action compared to the oxy-derivatives. For example, thiopentobarbital and thiamylal have much faster onsets and shorter durations than their respective oxy-congeners, pentobarbital and secobarbital, respectively (Fig. 15.4). Because thiobarbiturates have a specialized role as anesthetics, the reader is referred to Chapter 16 for further discussion of these agents.

PHARMACOKINETICS AND METABOLISM OF BARBITURATES Barbiturate salts that are approved for use as sedative-hypnotics are rapidly and completely absorbed following oral ingestion, in contrast to the free acids, which are absorbed at a much slower rate. The time of onset and duration of action are also significantly influenced by the lipophilicity of the individual agent and the route of administration. The five sedative-hypnotic barbiturates described here are all highly lipophilic, with corresponding logP values above 1.5, compared to barbital, which has a logP of 0.65 (Table 15.1) (29). Given the high proportion of cardiac output that is directed toward the brain, more lipophilic barbiturates are more rapidly distributed to the CNS and will have a faster time of onset. As with other CNS-acting agents, the time of onset is also dependent on the route of administration, with intravenous administration being the fastest and having near immediate effects, followed by intramuscular administration, which leads to faster brain distribution than the 10 to 60 minutes typical of orally administered sedative-hypnotics (Table 15.1).

Lipophilicity facilitates the relatively short duration of action of the barbiturates due to redistribution from the brain to other body compartments upon equilibration. This redistribution of barbiturates from the brain to other sites (e.g., adipose tissue) is the major mechanism that contributes to the loss of sedative-hypnotic activity of these agents, leading to durations of 3 to 8 hours for the short- and intermediate-acting agents and 10 to 16 hours for phenobarbital, which has the least lipophilicity and therefore the longest corresponding duration of action (Table 15.1). Because lipophilicity and route of administration can affect both time to onset and duration of action of barbiturates, these factors will influence a particular barbiturate's place in therapy. The anticonvulsant barbiturates are typically less lipophilic (e.g., phenobarbital) and correspondingly have slow onsets and long durations upon oral dosing, whereas the sedative-hypnotic agents described here are typically administered orally to achieve an optimum balance between achievement of sleep onset and duration. On the contrary, anesthesia-inducing barbiturates such as thiamylal are termed ultra-short acting due to their extremely high

TABLE 15.1 Pharmacokinetic Parameters of Barbiturates Approved for Sedative-Hypnotic Use

Barbiturate	R1	R2	LogP	Onset Time (min)[d]	Duration of action (hour)	Classification
Pentobarbital			2.10[a]	10–15	3–4	Short-acting
Secobarbital			2.36[b]	10–15	3–4	Short-acting
Amobarbital			2.07[d]	45–60	6–8	Intermediate acting
Butabarbital			1.60[b]	45–60	6–8	Intermediate acting
Phenobarbital			1.46[b]	30–60	10–16	Long-acting

[a] From Freese IE, Levin BC, Pearce R, et al. Correlation between the growth inhibitory effects, partition coefficients and teratogenic effects of lipophilic acids. Teratology. 1979;20:413–440.
[b] Average determinations from Slater B, McCormack, A, Avdeef A, et al. pH-metric log P.4. Comparison of partition coefficients determined by HPLC and potentiometric methods to literature values. J. Pharm. Sci 1994;83:1280–1283
[c] From Kakemi K, Arita T, Hori R, et al. Absorption and excretion of drugs. XXXI. On the relationship between partition coefficients and chemical structures of barbituric acid derivatives. Chem Pharm Bull. 1967;15:1705–17
[d] Upon oral administration.

lipophilicity (logP > 3), which confers immediate onset and very short durations upon intravenous injection.

Although loss of barbiturate sedative-hypnotic activity occurs primarily due to redistribution, the agents are also metabolically transformed. Metabolism of barbiturates is dependent on their individual degrees of lipid solubility—the more lipophilic compounds generally undergo greater metabolic transformations. It is important to understand that metabolism of barbiturates leads to metabolites that lack a high degree of lipophilicity and that, as a result, lack sedative-hypnotic activity. To achieve loss of lipophilicity, barbiturates are typically conjugated with glucuronide or sulfate conjugates that are hydrophilic and will allow for renal excretion of the agents. The most important pathway of barbiturate metabolism is oxidation or removal of the substituents at the 5-position carbon (Fig. 15.5). These phase 1 oxidation transformants are typically alcohols, or phenols in the case of phenobarbital, which can appear in the urine as either free or conjugated metabolites as a result of further phase 2 reactions leading to glucuronides or sulfates. The formed alcohols can also be further oxidized to yield ketones or carboxylic acid metabolites, which can be excreted freely or also conjugated (Fig. 15.5). Although not as significant as the route described earlier, oxidative desulfuration of thiobarbiturates can also occur, leading to more hydrophilic oxybarbiturates. Oxybarbiturate metabolites of thiamylal and thiopentobarbital are subsequently oxidized by the phase 1 and phase 2 reactions described earlier (Fig. 15.5).

Benzodiazepines

As with the barbiturates, benzodiazepines modulate the function of $GABA_A$ receptors, leading to neuronal hyperpolarization and CNS depressant effects. In contrast to the barbiturate binding site of $GABA_A$ receptors, the benzodiazepine binding site has been well characterized and is known to be formed by the interface of α and γ subunits. Not surprisingly, $GABA_A$ receptors that lack the γ subunit (e.g., $\alpha_6\beta\delta$) are completely insensitive to all benzodiazepines. Additionally, it has been shown that isoforms of the α subunit have differential benzodiazepine binding affinities, with the α_1 subunit–containing receptors (often termed BZ_1 receptors) having high benzodiazepine affinity and the α_2, α_3, and α_5 subunit–containing receptors (BZ_2 receptors) having

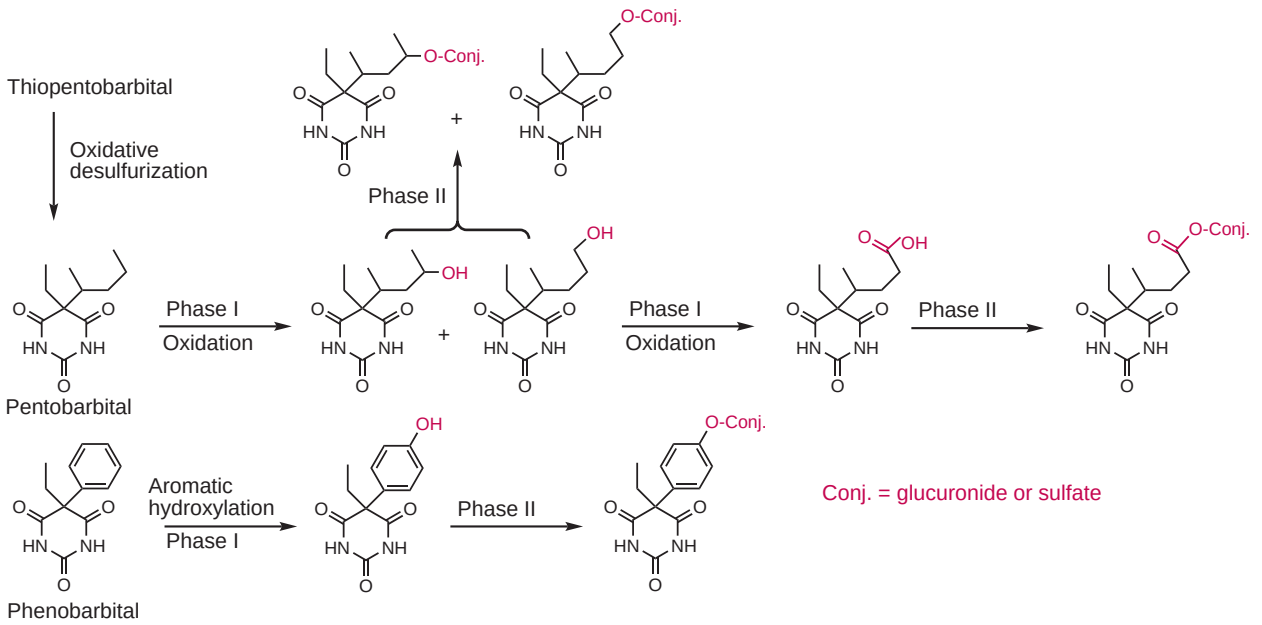


FIGURE 15.5 Major routes of metabolism of barbiturates. Thiopentobarbital and pentobarbital are used as examples to describe metabolism of alkyl thio- and oxybarbiturates, whereas phenobarbital exhibits the metabolism of an aromatic substituent. Coloration indicates site of metabolism.

moderate benzodiazepine affinity. Furthermore, some combinations that include α_4 or α_6 subunits are completely insensitive to benzodiazepine agonists, even in the presence of an appropriate γ subunit (20).

Binding of benzodiazepines to the allosteric BZ binding site can produce agonist, partial agonist, inverse agonist, or antagonist physiologic responses. Benzodiazepine agonists are used clinically as sedative-hypnotic agents as well as for the treatment of anxiety and convulsant disorders, in accordance with their ability to allosterically augment GABA-mediated inhibitory Cl^- conductance through the $GABA_A$ channel. Specifically, binding of benzodiazepines to the BZ site leads to increases in the binding-on rate and affinity of one GABA molecule to the first GABA binding site of the receptor (30–32). The increased affinity and rate of binding of GABA correlate with an increase in the frequency of the open-channel bursts. It is important to distinguish that benzodiazepines increase the frequency of channel opening, whereas barbiturates increase the duration of the open channel, and as such, the two classes of agents have distinct molecular effects on the $GABA_A$ receptor. Furthermore, benzodiazepines lack any effects in the absence of GABA, unlike the barbiturates. The reader is referred to Chapter 14 for more detailed descriptions of benzodiazepine binding and function.

Pharmacologic Effects of Benzodiazepines All benzodiazepines are capable of producing sedative-hypnotic effects; however, currently only five shorter acting benzodiazepine agents are approved by the FDA for use as sedative-hypnotics: estazolam, flurazepam, quazepam, temazepam, and triazolam. Residual hypnosis and psychomotor and cognitive inhibition are common side effects associated with their use. All of these agents are agonists of the BZ site of $GABA_A$ receptors containing α and γ subunits. Physiologically, all of the agents significantly reduce sleep latency and the number and duration of nighttime awakenings, resulting in an increase in total sleep time. The clinical use of these agents as sedative-hypnotics is not free from untoward effects, which are primarily manifested as excessive residual next-day sleepiness, tolerance upon long-term use, and withdrawal upon discontinuation. Another effect that is clinically important is the ability of benzodiazepines to produce a high degree of anterograde amnesia, in which recent events are not transferred to long-term memory (33).

Structure–Activity Relationships of Benzodiazepines The SARs of benzodiazepines are described in detail in Chapter 14, and the reader is referred to that chapter for the particulars of benzodiazepine binding requirements. Regarding the SAR of sedative-hypnotic benzodiazepines, all five agents contain the 5-phenyl-1,4-benzodiazepine-2-one backbone required for $GABA_A$ activity, and all include an electronegative 7-position chloro substitution as required on ring A (see Chapter 14 and Fig. 15.6). Similarly, all contain a pendant 5-phenyl ring (ring C) that is required for in vivo agonism and that can be substituted with ortho-electronegative halogens to increase lipophilicity, as is the case with flurazepam, quazepam, and triazolam. Interestingly, parasubstitution on ring C leads to inactive benzodiazepines, suggesting that steric restrictions are important at this site. Of note, several benzodiazepines, including

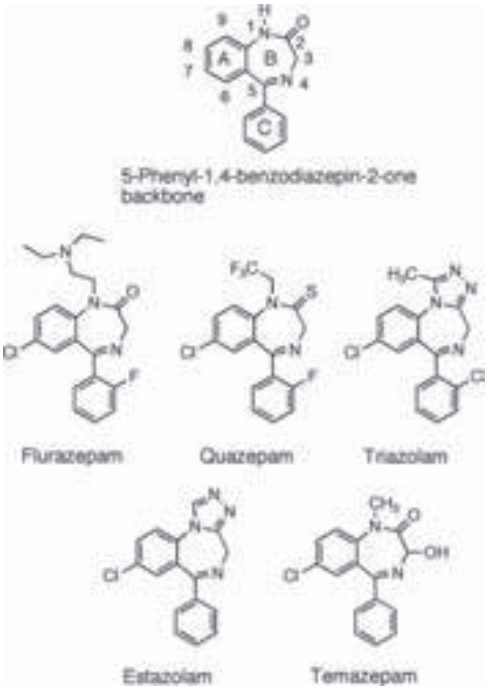


FIGURE 15.6 The benzodiazepine backbone and the benzodiazepines that are indicated for sedative-hypnotic use.

estazolam, are metabolized at the *para-* (4′) position, leading to inactivation of the agent. The major structural differences that impart distinct pharmacokinetic properties to the sedative-hypnotic benzodiazepines are located within ring B, the major site of metabolic transformation of these agents. The structural features of ring B that contribute to metabolism are discussed in the following section.

Pharmacokinetics and Metabolism of Benzodiazepines Benzodiazepine agents, like the barbiturates, are lipophilic and can be easily absorbed upon oral ingestion and rapidly distributed to the brain. Among the oral benzodiazepine formulations specifically indicated for the treatment of insomnia, flurazepam is absorbed most rapidly, achieving mean peak plasma concentrations within 0.5 to 1.0 hour. Temazepam and triazolam reach mean peak plasma concentrations within 0.5 to 2.0 hours, whereas estazolam and quazepam take longer (Table 15.2).

The sedative-hypnotic duration and side effect potential of benzodiazepines is greatly influenced by metabolism of the parent agent and the activity of resulting metabolites. Flurazepam has an elimination half-life of approximately 2 hours and is primarily metabolized by CYP3A4-mediated *N*-dealkylation and hydroxylation yielding active N^1-desalkyl and N^1-hydroxyethyl metabolites with elimination half-lives of 47 to 100 and 2 to 4 hours, respectively (Fig. 15.7, Table 15.2) (34). After a single 30-mg dose, the N^1-hydroxyethyl is undetectable in the plasma after 24 hours. On the contrary, levels of N^1-desalkylflurazepam are five- to sixfold higher after 7 days of administration than they are after 24 hours, suggesting buildup of this active metabolite. Conjugation of N^1-hydroxyethylflurazepam in phase 2 reactions allows for urinary excretion, and this conjugate is the major urinary metabolite accounting for up to 55% of a single dose (Fig. 15.7). The long half-life of these metabolites explains the clinical findings that flurazepam exhibits faster sleep latency and decreases in total wake time following several days of use and also why it is still efficacious for one to two nights following discontinuation of the parent. These observations are especially important in elderly populations, in whom the elimination half-life of *N*1-desethylflurazepam is significantly higher (up to 160 hours).

Quazepam is metabolized by microsomal CYP450 oxidases to yield 2-oxoquazepam, which is subsequently *N*-dealkylated to *N*-desalkyl-2-oxoquazepam (Fig. 15.7) (35). Both of these metabolites are pharmacologically active and have long durations, with mean plasma elimination half-lives of 40 and 73 hours, respectively (Table 15.2) (35). Both 2-oxoquazepam and *N*-desalkyl-2-oxoquazepam can be further hydroxylated at the 3-position, yielding 3-hydroxy-2-oxoquazepam and 3-hydroxy-*N*-desalkyl-2-oxoquazepam, respectively. These hydroxylated metabolites are inactive and can be *O*-glucuronidated and excreted readily in the urine (Fig. 15.7). As a consequence of the slow elimination of multiple active metabolites of both flurazepam and quazepam, residual hypnotic effects, including excessive daytime drowsiness, oversedation, and cognitive decline and confusion, are common and clinically relevant adverse effects.

These problems led to the development of newer triazolobenzodiazepines, such as estazolam and triazolam, with high $GABA_A$ receptor affinity and relatively shorter durations. The 1,4-triazolo ring of these congeners prevents oxidative metabolism typical of the benzodiazepines, which as in the case of flurazepam and quazepam results in formation of active metabolites with long elimination half-lives. The presence of the fused fourth ring of these agents also changes the numbering convention, such that numbering priority proceeds around the triazole ring (Fig. 15.8). Estazolam has a longer elimination half-life (10 to 24 hours) compared to flurazepam, but this agent is primarily metabolized by CYP3A4 yielding 4′-hydroxyestazolam as a major metabolite and 1-oxoestazolam as a minor metabolite (Fig.15.8, Table 15.2). Additionally, a 4-hydroxyestazolam metabolite has been identified in humans and is also detected in the urine at high levels (36). Although these metabolites have weak pharmacologic activity, three important factors prevent them from contributing to any significant sedative-hypnotic effects. The first is the low affinities of the metabolites for the $GABA_A$ receptor. In particular, 4′-hydroxestazolam is sterically hindered from optimal $GABA_A$ binding, consistent with SAR findings that parasubstitutions of ring C lead to decreased potency. The second factor that impedes the activity of estazolam metabolites is their decreased lipophilicity compared to the parent drug. This decrease facilitates the final

TABLE 15.2 Pharmacokinetic Parameters of Benzodiazepines Approved for Sedative-Hypnotic Use

Drugs	Trade name	Log P[a]	Time to peak conc. (hrs)	Parent elimination half-life (hrs)	Major metabolites (t1/2, hrs)	Predominant CYP isoform(s)
Flurazepam	Dalmane	2.35	0.5–1.0	2 ca.	*N*1-desalkyl (47–100, active) *N*1-hydroxyethyl (2-4, active)	3A4
Quazepam	Doral	4.03	2 ca.	39	2-Oxo (40, active) N-desalkyl (73, active)	3A4/2C9
Estazolam	Prosom	3.51	0.5–6.0	10–24	4'-Hydroxy; 4-Hydroxy; 1-Oxo (all inactive)	3A4
Triazolam	Halcion	2.42	<2	1.5–5.5	α-Hydroxy (50-100% active) 4-Hydroxy (inactive)	3A4
Temazepam	Restoril	2.19	1.2–1.6	0.4–0.6	O-glucuronide	–

[a] From Sangster Research Laboratories LOGKOW database

factor, which is that the circulating metabolites are found in low concentrations due to direct excretion of the hydrophilic free metabolites or their rapid *O*-glucuronidation, which readily allows for urinary excretion of the agents (Fig. 15.8).

Triazolam has a short duration of approximately 4 hours and is metabolized in humans to six metabolites, one of which, α-hydroxytriazolam, has been shown to retain 50% to 100% of the potency of the parent compound. Although only small amounts of the parent drug

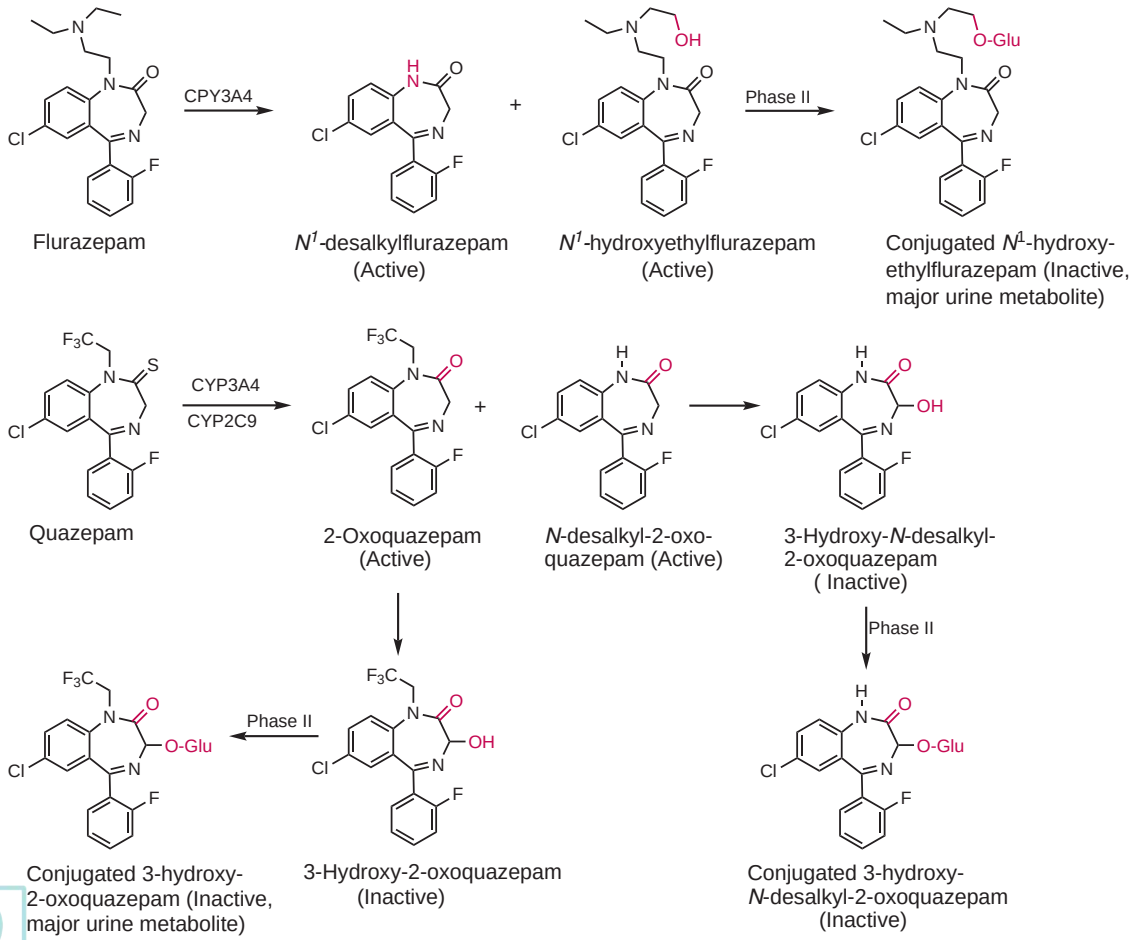


FIGURE 15.7 Metabolism of flurazepam and quazepam leads to formation of multiple long-acting active metabolites. Coloration indicates site of metabolism.

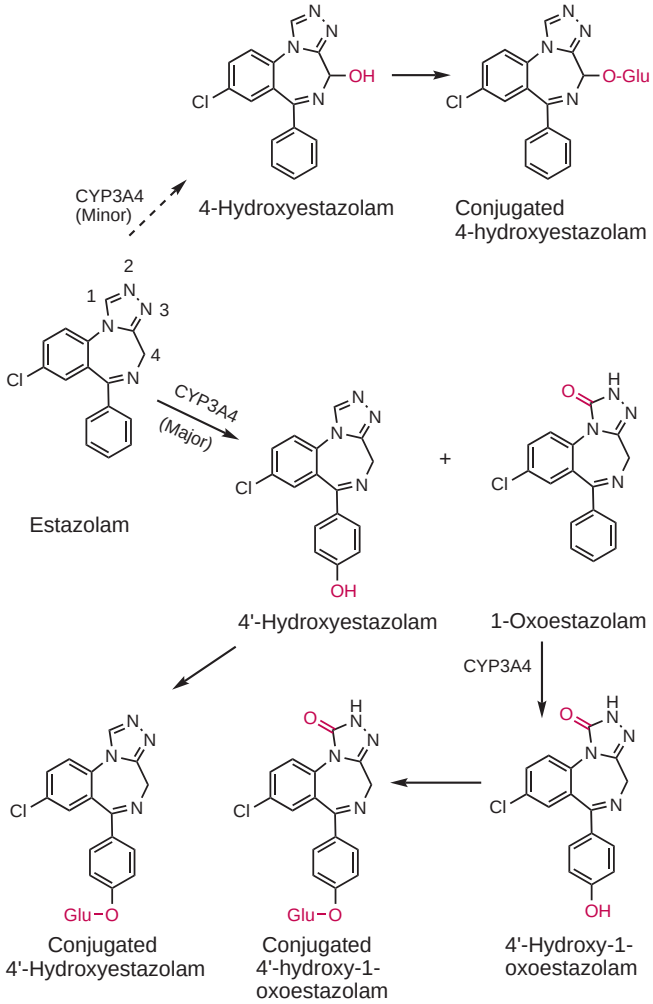


FIGURE 15.8 Metabolism of estazolam. Coloration indicates site of metabolism.

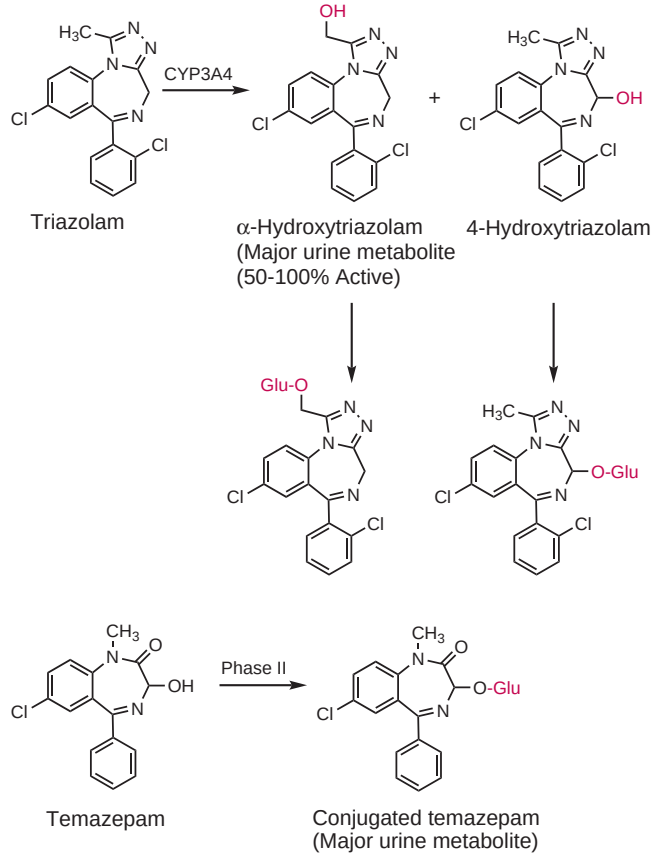


FIGURE 15.9 Metabolism of triazolam and temazepam. Coloration indicates site of metabolism.

are found in the urine, α-hydroxytriazolam and 4-hydroxytriazolam are the principal glucuronidated metabolites found in the urine, and these account for approximately 80% of triazolam excretion (Fig. 15.9) (37). There is no evidence of accumulation of triazolam metabolites, and the clinical effects of the active α-hydroxytriazolam are unclear because this metabolite has been detected in the plasma primarily in its glucuronidated form. Taken together, the relatively short half-life of the parent coupled with the urinary excretion of glucuronidated metabolites afford triazolam a relatively short duration of action compared with other benzodiazepines.

Temazepam is unique among the sedative-hypnotic benzodiazepines in that it contains a 3-hydroxy group, and as such, the agent circumvents phase 1 oxidation reactions prior to conjugation and excretion. This feature affords a 0.4- to 0.6-hour elimination half-life and rapid excretion of the parent, while also providing the additional benefit of bypassing oxidative hepatic metabolism (Fig. 15.9). Based on this route of metabolism, temazepam has no active metabolites. In fact, the only significant metabolites that have been described are the *O*-glucuronide of the parent, which is the major metabolite (>90%), and the *O*-glucuronide of *N*-desmethyltemazepam (<10%). Importantly, these products are formed independently of CYP450 isoforms and are rapidly excreted in the urine with half-lives of approximately 2 hours.

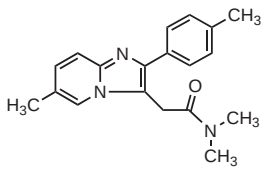
Benzodiazepines are used as sedative-hypnotic agents, as well as general muscle relaxants, anxiolytics, and anticonvulsants, yet as mentioned previously, their use can be confounded by presentation of undesirable side effects. Although death by benzodiazepine overdose is rare and typically only results as a consequence of concomitant use with other CNS depressants, these agents are not free from adverse effects and toxicities. Nearly all benzodiazepines have been reported to cause dose-dependent alterations in behavior, specifically bizarre, uninhibited, and confused behaviors. The propensity of benzodiazepines to cause tolerance and their potential for physical dependence and abuse also limit their use. Additionally, misuse of short-acting hypnotic benzodiazepines such as flunitrazepam (Rohypnol) has had profound social and medicolegal implications due to their use as "date rape" or "robbery" drugs. This elicit use is based on the ability to produce rapid hypnosis in combination with anterograde amnesia. In addition to cognitive effects, benzodiazepines may also exhibit respiratory depressant effects depending on the dose and the duration, and as such, they are contraindicated in patients with pulmonary conditions or sleep apnea. These

factors contributed to the development of nonbenzodiazepine sedative-hypnotics, which were devoid of many of the adverse effects induced by classical benzodiazepines.

Nonbenzodiazepine $GABA_A$ Agonists

Due to advances in molecular biology, genetics, and pharmacology in the late 1980s to early 1990s, numerous lines of evidence demonstrated that different $GABA_A$ receptor subtypes may bring about distinct functions depending on their localization in the brain. Future work revealed that α_2, α_3, and α_5 subtype–containing $GABA_A$ receptors (BZ_2) play critical roles in the anxiolytic, anticonvulsant, muscle relaxant, and cognitive impairment properties of classical benzodiazepines, whereas modulation of the α_1-containing $GABA_A$ receptor subtypes (BZ_1) was shown to be the key to benzodiazepine-induced sedation and hypnosis (38–42). Importantly, these findings revealed that it could be feasible to design functionally selective drugs that act as selective agonists at specific $GABA_A$ subtypes to yield the appropriate pharmacotherapeutic outcomes. For example, selective α_2- or α_3-acting agents could have anxiolytic properties while being devoid of sedative effects, whereas selective α_1-acting agents would behave specifically as sedative-hypnotic agents. Although classical benzodiazepines described here and in Chapter 14 are nonselective and demonstrate sedative-hypnotic, anxiolytic, and other effects, the discovery of novel nonbenzodiazepine compounds with a high degree of selectivity for α_1 subtype–expressing $GABA_A$ receptors allowed for the specific use of these agents as sedative-hypnotics. Currently, three structurally distinct nonbenzodiazepines—zolpidem, eszopiclone, and zaleplon, which are often referred to as the Z-drugs—are approved in the United States for treatment of insomnia, and several other investigational agents are in various stages of clinical trials.

Zolpidem



Zolpidem is an imidazopyridine that is a highly selective agonist of the α_1 subunit–expressing $GABA_A$ receptors (BZ_1), demonstrating 5- and 10-fold greater affinity for α_1 versus α_2 and α_3 subtypes, respectively (43). Similar to the benzodiazepines, zolpidem lacks appreciable affinity for α_4 and α_5 receptors (43). Of the three marketed nonbenzodiazepine drugs, zolpidem also has the greatest functional potency at potentiating GABA currents (44). The hypnotic effects of zolpidem parallel those seen for temazepam and triazolam, but based on its selective pharmacologic profile, zolpidem demonstrates weaker anxiolytic, anticonvulsant, and muscle relaxant effects compared to the classical benzodiazepines. Zolpidem has been shown to significantly improve sleep latency and prolong the duration of sleep in healthy volunteers and in patients with insomnia. Studies that compare the sleep outcomes of zolpidem with those of benzodiazepines have generally revealed comparable onset and sleep durations, while also showing that zolpidem leads to significantly fewer nighttime wakenings and, at the same time, does not cause residual morning sedation, confusion, or memory impairment (44–48). Further studies demonstrated that zolpidem exhibits significant improvements with regard to sleep latency, and subjective accounts indicated improved sleep quality compared to benzodiazepines. Extensive review of trial data that compare sleep outcomes of zolpidem to various benzodiazepines shows that zolpidem is comparable or superior to various benzodiazepines (49–51).

Zolpidem is currently available in the United States in two different formulations, immediate or controlled release. Oral administration of both formulations leads to bioavailability of approximately 70% and peak maximal plasma concentrations within 1.6 hours (Table 15.3). Although plasma concentrations of zolpidem begin to decrease at approximately 2 hours following administration of the immediate-release formulation, the extended-release formulation produces a more sustained peak plasma concentration that results in higher plasma concentrations over an 8-hour period. Direct comparison of the two formulations shows that plasma concentration profiles are generally identical for 2 hours following administration, after which decreases in blood levels are seen with the immediate-release formulation. The controlled-release formulation allows for this peak blood level to be extended for approximately 1 to 2 additional hours, affording correspondingly sustained blood levels throughout the night. Administration of the agent with food doubles the time required to reach peak and lowers the peak concentration by 30%. Accumulation of zolpidem does not seem to occur upon repeated exposure, regardless of the formulation. Recently, the FDA has approved a zolpidem oral spray formulation, which is distinguished by the fact that it allows for significantly faster time of onset of approximately 15 minutes (Table 15.3) and, as such, is clinically useful for patients with difficulties in achieving sleep initiation.

Structure–Activity Relationships of Zolpidem There have been many medicinal–chemical efforts that have attempted to define the SARs of zolpidem and to characterize interaction of the agent with the BZ_1 receptor. Anzini et al. (52) have integrated these models using the structurally similar, but non–α_1-selective, imidazopyridine anxiolytic agent alpidem. Based on these results, they have described a freely rotating aromatic ring region (FRAR), an electron-rich region (ERR), an antiplanar region (APR), and a planar aromatic region (PAR) (Fig. 15.10), which contribute to the binding of alpidem to BZ receptors. Studies on each of these regions have demonstrated that the replacement of alpidem's electronegative chloro groups at both the FRAR and PAR with methyl groups, as in zolpidem, does not affect receptor binding affinity, but significantly increases the selectivity for

TABLE 15.3 Pharmacokinetic Parameters of Nonbenzodiazepines Approved for Sedative-Hypnotic Use.

Drugs	Trade name	Log P[a]	Time to peak conc. (hrs)	Parent elimination half-life (mean hrs)	Major metabolites (t1/2, hrs)	Predominant CYP isoform(s)
Zolpidem	Ambien	2.31	Immediate-release 1.6[a]/1.6[b] Control-release 1.5[c] Oral spray 0.25	Immediate-release 2.5[a]/2.6[b] Control-release 2.6[c]	None active	3A4 (major) 2C9, 1A2, and 2D6 (minor)
Eszopiclone	Lunesta	−0.34	1	6.5	*N*-oxide (inactive) *N*-desmethyl (active, lower affinity)	1A2, 3A4
Zaleplon	Sonata	1.23	1	1	None active	3A4 (minor)

[a] 5 mg tablets.
[b] 10 mg tablets.
[c] 12.5 mg tablets.

α_1-subtype receptors (53). Further studies on the ERR have shown that conversion of either of the imidazole nitrogens to hydrogen bond donors leads to complete loss of selectivity for a1 subtype $GABA_A$ receptors (52). These data suggest a role for the imidazole nitrogen's ability to behave as hydrogen bond acceptors within the $GABA_A$ receptor binding site. (52). The importance of the ERR is also demonstrated by studies that convert the imidazole of zolpidem to its azaisostere congener. This simple change does not affect binding to α_1-subtype receptors but decreases binding to α_2 and α_3 such that potency at these subtypes is negligible, similar to that seen for the α_5 subtype (54). The antiplanar group has also been shown to be critical in facilitating binding to $GABA_A$ receptors by allowing for hydrogen bonding interactions. Molecular modeling studies have shown that the antiplanar carbonyl group of zolpidem can hydrogen bond to Ser^{204} or near Thr^{206}/Gly^{207} within the backbone of loop C of α_1 subunits, as well as to Arg^{194} within loop F of γ_2 subunits, which forms $\alpha_1\gamma_2$ complexes (55). Finally, the antiplanar group also contributes to binding selectivity and affinity, as sterically hindered bulky amide nitrogen substitutions show decreased binding to α_1-subtype receptors. This study also identified three additional α_1 and three additional γ_2 residues that are within 5 Å of zolpidem on molecular docking simulations, suggesting that other hydrogen-bonding or salt-bridge interactions can occur within the ligand binding domain.

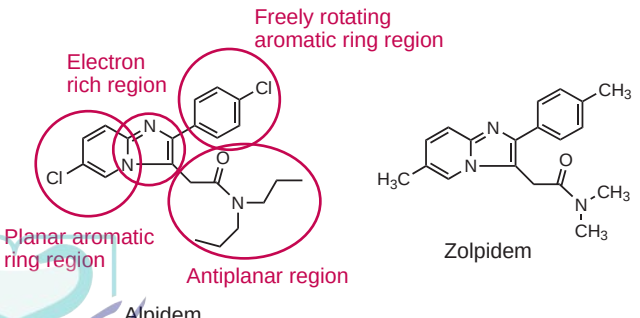


FIGURE 15.10 Structural relationship between of alpidem and zolpidem.

Metabolism of Zolpidem Zolpidem is rapidly eliminated, with a mean half-life of approximately 2.5 hours (Table 15.3). Repeated doses do not seem to accumulate, and elimination of the parent is achieved through extensive metabolism with only trace amounts of unchanged drug being found in urine or feces (56). In humans, zolpidem can be oxidatively metabolized to yield four primary metabolites, M II, M IV, M X, and M XI, all of which lack pharmacologic activity. As shown in Figure 15.11, the major metabolite is formed by CYP3A4-mediated hydroxylation of the *p*-tolyl methyl group yielding M III, which is subsequently oxidized to the corresponding carboxylic acid, M I (57). The M I metabolite is the principal metabolite found in human urine, accounting for approximately 70% to 85% of the administered dose. Microsomal enzyme-mediated hydroxylation of the *p*-methyl substituent on the imidazopyridine backbone can also occur, leading to formation of metabolite M IV, which can be further oxidized to the corresponding carboxylic acid M II, which accounts for approximately 10% of the administered dose. Importantly, M III was also shown to be formed by CYP2D6 and to a lesser degree by CYP1A2, whereas MI V formation by CYP1A2 and CYP3A4 was more modest (57). Because expression of CYP1A2 and CYP2D6 in human liver is generally significantly less than that of CYP3A4, the clinical contribution of these enzymes in transformation of zolpidem is expected to be minor. More recent studies have confirmed these suspicions and demonstrated that the contribution of CYP enzymes to zolpidem metabolism is greatest for CYP3A4 (61%), followed by CYP2C9 (22%), CYP1A2 (14%), and less than 3% for CYP2D6 (58). Because M III and M IV are not detectable in human urine or feces, but the respective carboxylic acids M I and M II are, it was proposed that rapid formation of these secondary metabolites occurs. Indeed, studies in rodents have demonstrated that the conversion of the alcohol metabolites to their corresponding acids occurs very rapidly and requires a nonmicrosomal enzyme, perhaps alcohol dehydrogenase (59). Finally, as shown in Figure 15.11, CYP3A4-mediated oxidation of zolpidem can also lead to formation of the M X and M XI minor metabolites, which are hydroxylated

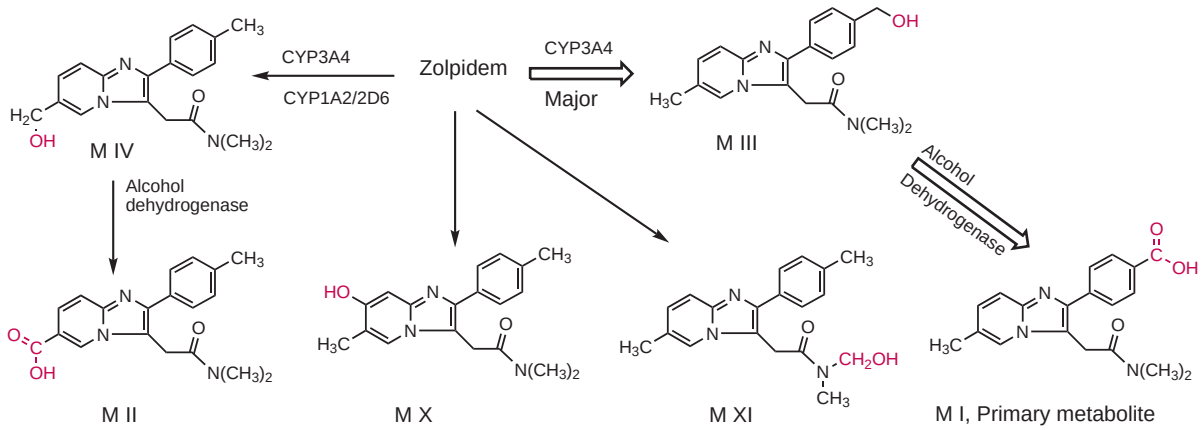
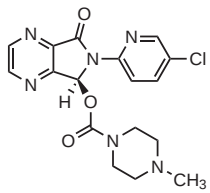


FIGURE 15.11 Metabolism of zolpidem. Coloration indicates site of metabolism.

on the imidazopyridine ring and the substituted amide nitrogen, respectively.

In elderly populations, dose adjustments must be made to account for the 50% increase in elimination half-life of the drug (60). Similarly, in patients with hepatic dysfunction, the plasma concentration of zolpidem doubles, with an increase in elimination half-life to a mean of 10 hours. Interestingly, there has been recent interest in the likelihood of differential gender-based metabolism of zolpidem based on the ability of testosterone to positively contribute to CYP3A4 activity such that higher circulating free testosterone increases CYP3A4 activity (60,61). Given this correlation, women are likely to have higher plasma concentrations of zolpidem and, as such, may be more likely to have higher degrees of zolpidem-mediated adverse effects (62).

Eszopiclone



(S)-Zopiclone

Eszopiclone, a pyrrolopyrazine cyclopyrrolone, is the active (*S*)-enantiomer of zopiclone, a racemic mixture that is no longer marketed in the United States. Eszopiclone significantly improves sleep latency and sleep maintenance, increases the time spent in stage III and IV sleep, and is distinguished by the fact that its approval is not limited to short-term utilization and that it has no potential for development of tolerance or abuse. Several trials have demonstrated that hypnotic efficacy is maintained and eszopiclone is well tolerated upon chronic dosing, lasting up to 12 months (63). In contrast to the racemic zopiclone, eszopiclone is devoid of substantial residual next-day sedative and cognitive effects. Unlike zolpidem, eszopiclone is not subtype selective. Yet, despite this lack of selectivity, it does not behave as classical benzodiazepines with respects to its pharmacodynamics and pharmacologic activity (see next section on SAR). Eszopiclone binds with higher affinity to α_1 receptors but also has appreciable affinity for α_3 subunits, and thus has hypnotic and other CNS activities. The affinity of the agent for α_1-subtype receptors is less than the other marketed nonbenzodiazepine agonists.

Eszopiclone is rapidly absorbed following oral administration, and peak plasma concentrations are reached within 1 hour with an elimination half-life of 6.5 hours, the longest of the nonbenzodiazepine hypnotics (Table 15.3). Similar to zolpidem, eszopiclone does not accumulate following repeated administration, and administration after a high-fat meal delays the time to peak plasma concentration by 1 hour and decreases this concentration by more than 20% (64). Eszopiclone dosing in the elderly must also be adjusted to account for 41% greater drug levels and a significantly longer half-life of 9 hours in this population. Similar dose adjustments must be made in patients with liver dysfunction as total exposure to eszopiclone increases twofold at the 2-mg dose, although the time to peak concentration and the concentration itself were unaffected (64).

Structure–Activity Relationships of Eszopiclone Eszopiclone (Fig. 15.12) exhibits 50-fold greater binding affinity for GABAA receptors than does the (R)-enantiomer. This leads to significant improvement in GABA potency, but more importantly, enantiomeric separation of the (S)-enantiomer seems to reduce adverse effects such as residual sedative effects seen with racemic zopiclone, despite the fact that the racemic mixture has a shorter half-life (5.0 vs. 6.5 hours). Racemization of one enantiomer to the other does not occur in mammals in vivo. Although SAR studies for cyclopyrrolones have not been performed to a great degree, it is known that this subclass recognizes a distinct site of the GABAA receptor complex that is allosteric to the recognition site for classical benzodiazepines (65). The regional distribution and specificity of sites labeled by radiolabeled cyclopyrrolones are similar to those labeled by classical benzodiazepine ligands, suggesting that the cyclopyrrolone binding site resides on the BZ site of the GABAA complex (65). However, unlike classical benzodiazepine agonists, binding of cyclopyrrolones is not affected by GABA or barbiturates. Furthermore, radioreceptor displacement binding studies revealed a noncompetitive

interaction of cyclopyrrolones at sites labeled by classical benzodiazepines, whereas displacement of radiolabeled cyclopyrrolones by classical benzodiazepines occurred competitively, suggesting that cyclopyrrolones recognize a site on the BZ receptor complex that is allosteric to the recognition site of classical benzodiazepines (65). Others have suggested that perhaps cyclopyrrolones can interact with one of multiple BZ binding sites on the GABAA receptor and, in doing so, cause allosteric changes in the ligand affinity at the remaining sites, potentiating further binding (66). With regard to binding within the ligand recognition site, molecular modeling and mutagenesis studies have shown that eszopiclone is within 4 Å of many amino acid residues within the GABA-BZ complex binding pocket, and such proximity allowed anchoring and stabilization by multiple hydrogen bond interactions with Arg144, Tyr209, Tyr159, and various other residues (55). These studies also revealed that the structural requirements for eszopiclone binding are different than those of zolpidem, and these differences may account for the lack of selectivity of eszopiclone (55).

Metabolism of Eszopiclone Eszopiclone is metabolized extensively by CYP3A4 and CYP1A2 isozymes, which yield the primary metabolites (*S*)-*N*-desmethylzopiclone and (*S*)-*N*-oxidezopiclone, respectively. The oxide metabolite is inactive, whereas *N*-desmethylzopiclone exhibits lower potency and affinity at $GABA_A$ receptors and therefore has only very weak hypnotic activity compared to the parent (Fig. 15.12). Interestingly, due to its lower affinity and lack of subtype selectivity, together with its weak sedative effects, this metabolite has been investigated as a novel anxiolytic agent (67). Only small amounts (<7%) of unchanged eszopiclone are excreted in the urine, and greater than 75% of a dose is excreted via this route as inactive transformants of the two primary metabolites.

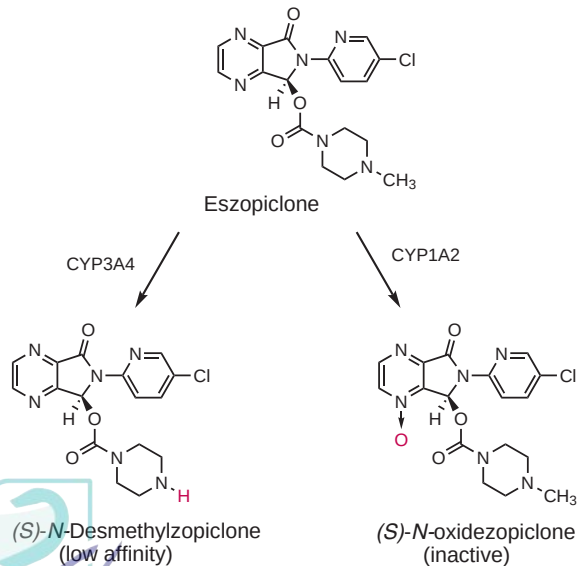
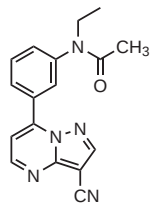


FIGURE 15.12 Metabolism of eszopiclone. Coloration indicates site of metabolism.

ZALEPLON



Zaleplon, a pyrazolopyrimidine, is a hypnotic agent that has a pharmacologic profile similar to zolpidem but is primarily distinguished by its extremely rapid onset and short half-life. Similar to zolpidem, zaleplon has greater affinity at the α_1- versus α_2- and α_3-containing receptors, albeit with one-third to one-half the potency of zolpidem (68). Unlike zolpidem, which does not recognize α_5-containing receptors with any appreciable affinity, zaleplon is able to potentiate the effects of GABA at α_5-containing receptors; however, its affinity for α_5-containing receptors is approximately 15-fold less than for α_1-containing receptors (68). Hence, zaleplon is considered an α_1-selective GABA modulator, which lacks the classical benzodiazepine effects on sleep.

The distinguishing features that afford zaleplon a unique place in the therapy of insomnia are its rapid rate of onset combined with its relatively faster rate of excretion. Oral administration of zaleplon leads to a mean peak plasma concentration in less than 1 hour, regardless of dose, the fastest of the nonbenzodiazepines (69). Although zaleplon is completely absorbed following oral administration, it is subject to first-pass metabolism, leading to an absolute bioavailability of 30% (Table 15.3) (69). As with zolpidem and eszopiclone, administration with heavy meals, particularly high-fat foods, delays the time to peak plasma concentration to 3 hours and reduces the peak plasma concentration by 35% (70,71). Following oral administration, zaleplon is rapidly eliminated with a mean elimination half-life of 1 hour, an effect that is delayed significantly in patients with hepatic dysfunction. Taken together, these pharmacokinetic properties facilitate the rapid onset and short duration hypnotic effects (70,71).

Clinically, zaleplon is distinguished by its ability to significantly reduce sleep latency for up to 5 weeks compared to placebo, an effect that can be contributed to its rapid onset (71,72). However, numerous clinical trials have failed to consistently show that a 50 or 10-mg nightly dose of zaleplon significantly improves sleep duration, decreases the number of awakenings, or improves overall sleep quality compared with placebo, likely due to the short half-life of the agent, which precludes hypnotic effects throughout the night. Higher nightly doses of zaleplon (20 mg) do significantly improve either sleep latency or duration, but effects on total sleep quality and number of awakenings compared to placebo have been inconsistent in clinical trials at this dose (71). Tolerance and withdrawal effects have not been reported during short-term treatment (up to 5 weeks), and the agent also seems to be free from rebound insomnia and residual next-day sedative effects, similar to other nonbenzodiazepine hypnotics (72). As a result of

these effects, zaleplon is approved only for patients with difficulties falling asleep; however, an extended-release formulation that could improve sleep maintenance and duration has been under development for some time.

Structure–Activity Relationships of Zaleplon Unlike for zolpidem and eszopiclone, extensive studies that examine the SARs of zaleplon have not been performed with regard to binding potency and interaction within the binding pocket. However, there have been numerous studies that compare the binding and function of zaleplon to the closely related compound indiplon (Fig. 15.13), allowing for deduction of SAR from pharmacologic results. These studies show that zaleplon exhibits approximately 7- and 10-fold greater selectivity for α_1- over α_3- and α_5-containing $GABA_A$ receptors, respectively, whereas indiplon demonstrates only 1.6- and 4-fold selectivity (73). Importantly, indiplon has 3-, 12-, and 7-fold higher affinity at α_1-, α_3-, and α_5-containing receptors, respectively, than does zaleplon. Further work has demonstrated that indiplon is greater than 100-fold more potent than zaleplon at potentiating GABA currents through α_1-containing receptors but is also 46- and 25-fold more potent at doing so through α_3- and α_5-containing receptors, respectively (44,73). This work suggests that the thiophene-2-carbonyl moiety of indiplon (Fig. 15.13) drives higher binding affinity and thus potency, but decreases overall selectivity for one subtype over another. Meanwhile, zaleplon contains only a cyano group at this position, suggesting that electronic rather than steric factors influence selectivity.

Metabolism of Zaleplon As described earlier, zaleplon is subjected to significant first-pass metabolism, which accounts for its low oral bioavailability. Following oral administration of the agent in humans, less than 0.1% of the drug is recovered unchanged in the urine. Animal studies have demonstrated distinct interspecies variability in metabolism of orally administered zaleplon due to interspecies differences in activity of hepatic aldehyde oxidase, which is the principle metabolic enzyme responsible for transformation of zaleplon (74). In rodents and canines, which have decreased expression and activity of aldehyde oxidase, zaleplon is predominantly metabolized by CYP3A4 to *N*-desethylzaleplon, with only minor oxidation of zaleplon by aldehyde oxidase to yield 5-oxozaleplon. In humans, these metabolic routes are interchanged due to greater activity of aldehyde oxidase, and as a result, the major metabolite is 5-oxozaleplon, whereas CYP3A4-mediated transformation, yielding *N*-desethylzaleplon, is a minor route (Fig. 15.13). Both primary metabolites are inactive and, once formed, can either be directly eliminated in the urine or oxidized further and excreted as a glucuronide conjugate. In addition, the *N*-desethylzaleplon metabolite can be rapidly converted, presumably also via aldehyde oxidase, to 5-oxo-*N*-desethylzaleplon (Fig. 15.13) (70). Following oral administration of radiolabeled zaleplon to healthy volunteers, 70% of the dose is recovered in the urine within 2 days, almost exclusively as the two primary metabolites or their glucuronide conjugates (70). The 5-oxozaleplon metabolite

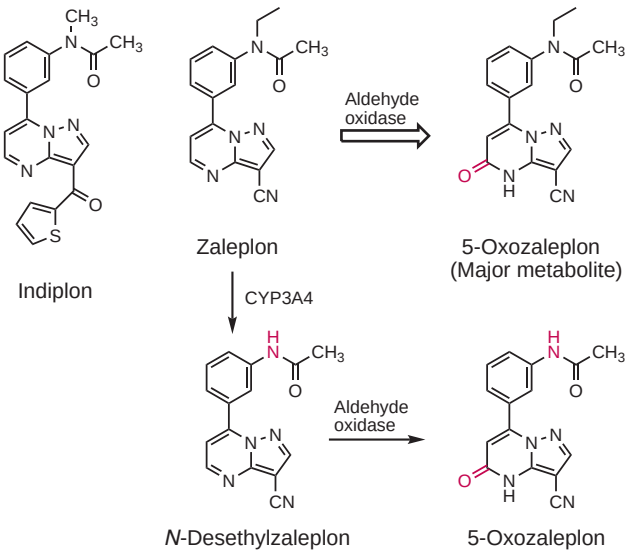


FIGURE 15.13 Structural relationship of zaleplon to indiplon and metabolism of zaleplon. Coloration indicates site of metabolism.

also predominates in the feces, where more than 15% of an administered dose can be found within 6 days.

The nonbenzodiazepines represent major advancements in treatment of insomnia. They are highly effective hypnotic agents with negligible residual daytime drowsiness and are generally free from the psychomotor and cognitive side effects of classical benzodiazepines. Despite their primary use at nighttime and their relatively short half-lives, these agents are also not completely devoid of adverse effects. Recently, there has been an increase in reported occurrences of nonbenzodiazepine-induced sleepwalking and associated amnesic sleep-related complex behaviors such as sleep driving, sleep eating, sleep cooking, sleep talking, and sleep sex (75–83). These effects have been reported at therapeutic and supertherapeutic doses and are potentiated by alcohol consumption. Importantly, patients do not have any recall or memory of these events. Although these unintended effects are rare, they are potentially very serious because they can affect social, emotional, and physical health and pose risks for fatal incidents.

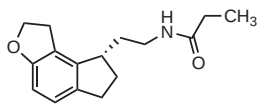
Melatonin Receptor Agonists

As described previously, melatonin is a neurohormone that is primarily synthesized in the pineal gland from its precursor serotonin (Fig. 15.1). Because melatonin synthesis is concurrent with sleep, the increase in endogenous nighttime melatonin levels correlates with the onset of sleepiness. The sleep-promoting and circadian effects of melatonin are due to agonism of both MT1 and MT2 receptors (MT1R, MT2R), both of which are present in very high density (~4 fmol/mg protein) within the SCN (84). Agonism of SCN MT1 receptors directly facilitates inhibition of SCN neuron firing promoting sleep, whereas activation of SCN MT2 receptors affects the circadian rhythm settings related to the central clock (85,86).

Melatonin itself is a poor chemotherapeutic agent due to its poor absorption and low oral bioavailability of less than

10%, as well as its ubiquitous effects on sleep and circadian rhythms. Moreover, because melatonin is a supplement that is not regulated by the FDA, preparations vary in their purity and concentration, and as a result, poor sleep outcomes are often encountered. The significant effects of MT receptor agonism on sleep coupled with the relatively poor nature of melatonin as a drug prompted intense medicinal–chemical efforts to develop novel small-molecule congeners of melatonin that behave as potent agonists of MT receptors. These efforts led to the successful launch of the first in-class melatonin receptor agonist (*S*)-ramelteon, which has an excellent sleep and safety profile. Other investigational MT agonists, such as tasimelteon, are also being developed for treatment of insomnia.

Ramelteon (Rozerem)



(*S*)-Ramelteon

(*S*)-Ramelteon (TAK-375) selectively binds to both MT1R and MT2R, recognizing the human receptors with extremely high affinity of 14 and 112 pmol/L, respectively, exhibiting 8- to 10-fold greater affinity for MT1R compared to MT2R and 6-fold greater affinity than melatonin for MT1R (87). The high potency and slight preference for MT1R correlate to the ability of the drug to primarily reduce sleep latency as opposed to regulation of phase-circadian rhythms. With regard to functional pharmacology, in Chinese hamster ovary cells ectopically expressing the human MT1R and MT2R, ramelteon was 4- and 17-fold more potent at inhibiting cyclic AMP production compared to melatonin, respectively, consistent with observations that demonstrate coupling of MT receptors to $G\alpha_{i/o}$ proteins (87). Moreover, ramelteon does not have any appreciable affinity for a third physiologically relevant melatonin binding site known as MT3R, which is a melatonin-sensitive quinine reductase that is not involved in the sleep/wake functions (88,89). Taken together, the absence of binding to brain receptors other than MT1R/MT2R and the potent activity of ramelteon at these melatonin receptors make ramelteon an efficacious sleep-inducing agent that is free from many of the CNS side effects common to other sedative-hypnotics.

Animal studies demonstrate that ramelteon significantly decreases wakefulness and increases both short-wave and REM sleep compared with placebo (88,90). In clinical trials, no effects on short-wave sleep have been noted, but the agent leads to significant decreases in sleep latency and increases in total sleep duration over a 5-week period compared to placebo (91–93). Importantly, ramelteon, consistent with its melatonin receptor–related mechanism, which is free of endogenous GABAergic signaling, does not produce residual next-day sedation or decreases in psychomotor function (93). Likewise, due to its unique mechanism, ramelteon does not hinder learning, cognition, and memory like the benzodiazepine agents do, and it also lacks the potential for abuse, does not lead to tolerance, and poses no risk of withdrawal or rebound insomnia upon discontinuation (92–94). One potential adverse effect that can be predicted for melatonin receptor agonists is based on the ability of melatonin to influence prolactin and testosterone levels via agonism of MT1 and MT2 receptors located within endocrine and reproductive tissue. Similarly, ramelteon has been reported to affect mean free and total testosterone levels (88). Further studies are necessary to gauge the clinical consequences, if any, that exogenous melatonin receptor agonists have on endocrine and reproductive function. In summary, from a sleep therapy standpoint, melatonin receptor agonists such as ramelteon have highly efficacious hypnotic effects while being free of many of the cognitive and residual effects common to $GABA_A$ modulating agents.

Structure–Activity Relationships of Ramelteon SARs for melatonin and its congeners have been reviewed at length previously (95–98). Early studies demonstrated that the indole backbone of melatonin was not required for activity so long as it was replaced by an aromatic isostere as in ramelteon (which contains an indane) or as in the investigational MTR agonists tasimelteon and agomelatine, which are currently undergoing clinical trials for treatment of insomnia (Fig. 15.14) (99). It has been proposed that the importance of the aromatic ring system here is to offer optimum distance between the amide side chain at position 3 and the 5-methoxy substitution (100,101). The aromatic moiety has also been suggested to interact with aromatic receptor residues within the binding pocket through *pi–pi* stacking. Although the aromatic portion contributes to spacing and likely *pi–pi* interactions, the 3-position amide and the 5-methoxy side chains are responsible for binding and functional activation of the receptors by interacting with two proposed binding pockets. The amide group is critical for agonist activity at both MT receptors and is thought to interact with key serine (Ser^{110} and Ser^{114}) and asparagine (Asn^{175}) residues in transmembrane helix (TMH) III of MT1 and TMH IV of MT2, respectively (102). Meanwhile, the 5-methoxy moiety is critical for functional effects. It has been proposed that the methoxy oxygen interacts with His^{195} and His^{208} within TMH VI of MT1R and MT2R, respectively (101,103). Movement of the methoxy group to the 4-, 6-, or 7-positions significantly decreases functional activity, suggesting that distance to these conserved histidine residues is critical in maintaining binding affinity and functional activity (97). Additionally, Val^{192}, which is located nearly one turn above His^{195} within the ligand binding domain has been shown to be involved in binding the methyl component of the methoxy group (101). Finally, the binding pocket of MTRs is highly stereoselective, an important feature that must be considered for drug design. As a consequence of the three-dimensional requirements of binding to MT receptors, ramelteon is dispensed as the enantiomerically pure (*S*)-enantiomer, which has 500-fold greater affinity for MT1 than does (*R*)-ramelteon.

Metabolism of Ramelteon (*S*)-Ramelteon is rapidly absorbed after oral administration, and mean peak plasma concentrations are achieved at 0.75 hours. In a study in healthy volunteers who were administered radiolabeled ramelteon, 84% of recovered radioactivity was found in the urine and 4% in the feces, suggesting that at least 84% of the drug was absorbed. However, ramelteon is subject to extensive first-pass metabolism, leading to an absolute oral bioavailability of only approximately 2% (104). Ramelteon has a short elimination half-life of 1 to 2.5 hours, and once-nightly dosing does not lead to accumulation of the drug. The time to peak plasma concentration was delayed by 45 minutes upon administration with food, and the peak plasma concentrations were decreased by 22% in this case (104). Ramelteon is primarily metabolized by oxidation in phase 1 reactions, with secondary metabolites being excreted as glucuronide conjugates (105). Hepatic CYP1A2 is the major isoform responsible for transformation (49%), whereas CYP2C19 (42%) and CYP3A4 (8.6%) isoforms are also contributors to ramelteon metabolism in the liver. On the contrary, in the intestines, only CYP3A4 contributes to transformation (106). The major metabolite of ramelteon in humans is the hydroxylated propionamide M II metabolite (Fig. 15.15), which is active, has a 2- to 5-hour half-life, and has 20- to 100-fold greater systemic exposure than that of the parent, suggesting slower removal from the circulation (104,105). Moreover, this metabolite has one-fifth to one-tenth the binding affinity of the parent for human MT1 and MT2 receptors and shows potent hypnotic effects in animals, suggesting that it may contribute to the sedative-hypnotic effects of ramelteon (88). In addition to the M II metabolite, ramelteon can be oxidized to the ring-opened M I metabolite or transformed to a keto-metabolite, M III (Fig. 15.15), both of which are inactive. Biotransformation of the M II and M III metabolites by sequential oxidation steps can lead to formation of M IV. The rank order of prevalence of the four metabolites in human serum is M II, M IV, M I, and M III, and all three of the hydroxylated metabolites can be excreted as glucuronide conjugates (Fig. 15.15). Importantly, ramelteon is also subject to a significant drug interaction upon coadministration with the antidepressant fluvoxamine, a strong CYP1A2 inhibitor. Coadministration of these agents leads to a greater than 100-fold increase in total systemic exposure of ramelteon and should be avoided.

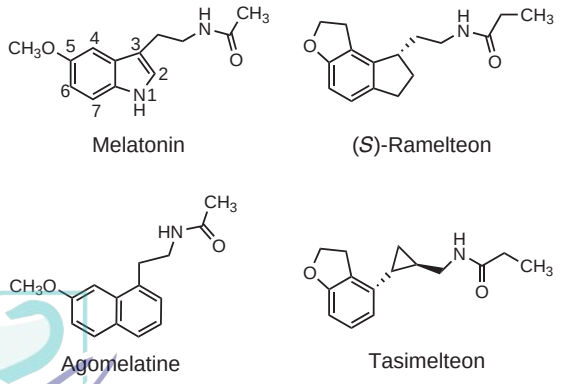


FIGURE 15.14 Structures of melatonin and the melatonin receptor agonists (*S*)-ramelteon, agomelatine, and tasimelteon.

Histamine H_1 Receptor Antagonists

The first generation of ethanolamine ether histamine H_1 receptor antagonists (i.e., antihistamines) that cross the blood–brain barrier are used for acute insomnia due to their sedation-promoting side effects. In particular, diphenhydramine and doxylamine, both high-affinity (low-nanomolar) H_1 receptor antagonists, are sold as over-the-counter sleep aids. Recently, the tricyclic antidepressant doxepin, which is a potent subnanomolar affinity H_1 antagonist, has also been approved for treatment of insomnia at lower doses than those used for depression (Silenor). The benefit of these agents for treatment of insomnia comes from H_1 receptor antagonism within the TMN of the posterior hypothalamus, where the normal release of histamine during the day causes arousal, and its decreased release at night reduces arousal responses. Antagonism of H_1 receptors within the TMN promotes sedation and drowsiness by inhibiting TMN outflow to other brain structures such as the dorsal raphe nucleus, paraventricular nucleus and locus coeruleus. Overall, antihistamines bring about increased drowsiness and sedation with marginal beneficial effects on sleep latency and total sleep time. There is very little in the way of rigorous clinical trial data that support their sedative-hypnotic efficacy, and to the contrary, some results reveal that these agents disrupt sleep architecture by delaying the onset to, and duration of, REM sleep. Regardless, these drugs are used heavily as sedative-hypnotics, and in the case of diphenhydramine and doxylamine, patients are able to readily self-medicate due to the ease in their availability. While diphenhydramine, doxylamine, and doxepin also exhibit antimuscarinic activity, leading to corresponding side effects such as dry mouth, urinary retention, vand blurred vision, a major side effect of these agents is excessive daytime drowsiness and residual next-day sedation, which are not uncommon. These next-day effects can lead to impaired cognition and performance and are attributed to the relatively longer half-lives. Finally, nightly use of first-generation antihistamines as sleep aids has been associated with tolerance to the hypnotic effect over long-term use. These agents are discussed further with respects to their SARs and metabolic transformations in Chapter 32.

FUTURE SEDATIVE-HYPNOTICS

As demonstrated within this chapter, $GABA_A$ receptor–acting hypnotics continue to be the mainstay for the pharmacotherapeutic management of insomnia. Although the pharmaceutical industry has a number of newer nonbenzodiazepine $GABA_A$ agonists such as indiplon under development, these agents are likely to have similar pharmacologic profiles as the currently used Z-drugs. The arrival of ramelteon to the marketplace was a major advance in development of sedative-hypnotics because it represented the first new class to be approved in several decades. Despite this relative paucity of novel sedative-hypnotics, there are several promising new CNS targets that have been exploited for their effects on the sleep/wake cycle, including 5-HT_{2A}, orexin, and neuropeptide S (NPS) receptors. As a result, the pharmaceutical industry

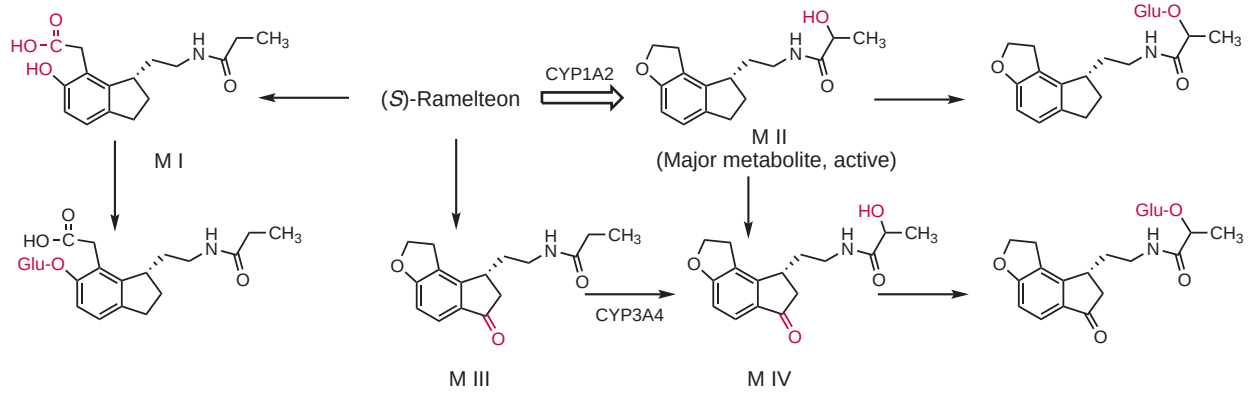


FIGURE 15.15 Metabolism of (*S*)-ramelteon. Coloration indicates site of metabolism.

has developed small-molecule antagonists of these targets with the hope of inducing and promoting sleep. Ritanserin, eplivanserin, and esmirtazapine are all 5-HT_{2A} receptor antagonists that are currently under investigation in various stages of clinical trials for treatment of insomnia. Because the effects of serotonin in the human brain are both broad and profound, further studies with these agents should shed light on the complexities of this system in regard to its regulation of the sleep/wake cycle.

Numerous lines of preclinical evidence support a key role of the orexin neuropeptides in promotion of wakefulness and alertness. Orexin neurons have been shown to extensively innervate key sleep/wake-regulating brain regions, in particular, the histaminergic neurons of the TMN. Binding of orexins to their cognate GPCRs, OX1 and OX2, has been demonstrated to promote wakefulness and alertness, suggesting that orexin receptor antagonism may have opposite effects. Indeed, almorexant is a first-in-class orexin receptor antagonist that is currently in phase III clinical trials for treatment of insomnia. This agent exhibits potent hypnotic effects in animals and humans, including those with insomnia, with minimal adverse effects and tolerability issues, suggesting that orexin receptor antagonism may provide a unique approach to treat insomnia.

Similarly, NPS is another recently described neuropeptide that is expressed in distinct brain regions, most notably in the locus coeruleus. As with the orexins, injection of NPS has been found to significantly increase wakefulness and suppress all stages of sleep. These effects are mediated by the recently discovered NPS receptor, another GPCR, and suggest that antagonism of NPS receptors could lead to a hypnotic effect. Because GPCRs are relatively amicable drug targets—approximately 40% to 50% of all marketed drugs target a GPCR—these novel targets offer promising strategies for the development of new sedative-hypnotic agents.

SCENARIO: OUTCOME AND ANALYSIS

Outcome

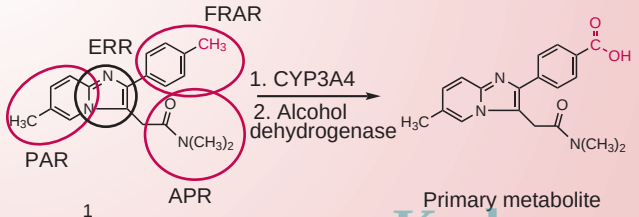
Susan W. Miller, PharmD, CGP, FASCP

The pharmacist's review concluded that one of the warnings associated with the use of zolpidem includes new onset of behavioral changes and complex behaviors. Sleep-eating is one of these complex behaviors and the consumption of additional food may account for the weight gain and the elevated hemoglobin A_{1C} level. The pharmacist's recommendations for the MTM were to taper the zolpidem over 4 days to discontinue its use and to initiate therapy with ramelteon dosed at 8 mg po 30 minutes before bedtime on day 5 of the taper. (Use of ramelteon is also associated with the development of complex behaviors.) The pharmacist also recommended discontinuation of the itraconazole because of the potential for drug interaction with the verapamil and zolpidem (now discontinued) and initiation of topical therapy with ciclopirox for treatment of the fingernail onychomycosis. WK should continue to monitor her diabetes and weight and return for a follow-up visit in 3 months. No changes were suggested for the diabetes or hypertension therapies at this time.

Chemical Analysis

S. William Zito and Victoria Roche

Zolpidem is an imidazopyridine, which is a highly selective agonist of the α_1-subunit of the $GABA_A$ receptors. SAR studies have revealed four regions responsible for zolpidem's binding to the $GABA_A$ receptors: 1) the freely rotating aromatic ring (FRAR), 2) an electron-rich region (ERR), 3) an antiplanar region (APR), and 4) a planar aromatic region (PAR). The methyl substituents found on FRAR and PAR regions and the hydrogen-bond–accepting imidazole nitrogen are responsible for zolpidem's α1 selective ability.



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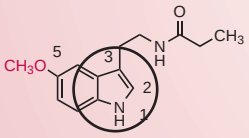
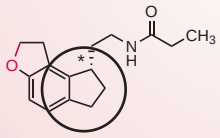
SCENARIO: OUTCOME AND ANALYSIS *(Continued)*

Zolpidem is a short-acting nonbenzodiazepine hypnotic that works like the BZs by binding to the γ-aminobutyric acid receptors. Zolpidem is used for the short-term treatment of insomnia. It works quickly (usually within 15 minutes) and has a short half-life (2 to 3 hours). The onset of zolpidem toxicity (behavioral changes and complex behaviors such as sleep-eating) is most likely caused by the addition of itraconazole, which is a CYP 3A4 inhibitor. Because zolpidem is metabolized by CYP 3A4, its metabolism will be inhibited by itraconazole and lead to behavioral toxicity.

Ramelteon is an analog of melatonin, the biological activity of which is related to circadian rhythm and induction of sleep. There are three melatonin receptors (MT1, MT2, and MT3) found in the CNS. MT1 is associated with induction of sleep and MT2 with setting the body's "biological clock." The role for MT3 has yet to be determined. Ramelteon changes the indole ring of melatonin to an indane ring and constrains the 5-methoxy group into a furan ring to form an indenofuran moiety.



Melatonin

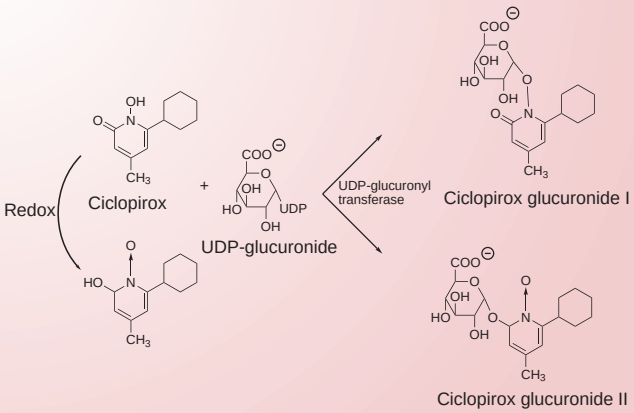


Ramelteon

The amide side chain on position 3 is critical for agonist activity at both MT1 and MT2 receptors. Ramelteon contains a stereochemical center at position 3 and the (*S*)-enantiomer has 500-fold greater affinity for MT1 than does (*R*)-ramelteon.

Ramelteon is primarily metabolized by phase I oxidation followed by excretion of the glucuronide conjugates. CYP1A2 is the major isoform responsible for transformation (49%), whereas CYP2C9 (42%) and CYP3A4 (8.6%) isoforms also contribute. The low percent of metabolism of ramelteon by CYP3A4 would not preclude the use of itraconazole; however, because WK is taking verapamil, which is metabolized by CYP3A4, the decision to discontinue itraconazole is justified.

Ciclopirox is a hydroxylated pyridinone that is used topically to treat superficial dermatophytic infections, primarily onychomycosis. Ciclopirox has a unique mechanism of action through chelation of polyvalent cations, such as Fe^{3+}, which causes inhibition of a number of metal-dependent enzymes within the fungal cell. Ciclopirox is metabolized by phase II glucuronidation and does not inhibit any CYP450 isoforms and would not interfere with the metabolism of the other of WK's medications.

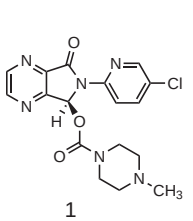


CASE STUDY

S. William Zito and Victoria Roche

BB is a 40-year-old school teacher who suffers from chronic insomnia. She experiences 3 to 5 awakenings every night and then finds it difficult to fall asleep again. She also experiences daytime fatigue and is unable to concentrate on her teaching responsibilities. Upon questioning, BB vaguely remembers being involved in a stressful family inheritance dispute years ago just before the onset of her sleep difficulty. BB also reports anxiety at bedtime because of the prospect of another sleepless night. BB has a history of hypertension, which is under control by treatment with diltiazem HCl (480 mg daily) and enalapril maleate (10 mg daily).

BB has been diagnosed with psychophysiological insomnia, sometimes referred to as "behavioral insomnia." The mainstay of treatment for this type of chronic insomnia is behavioral therapy, which can take 2 to 3 months to learn and provides clinical benefit. BB's physician wants to prescribe a sedative-hypnotic treatment until she experiences the benefits of the behavioral therapy. Evaluate the three choices for use in this case, given below.



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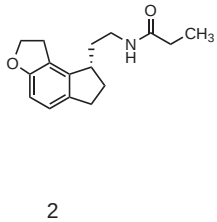

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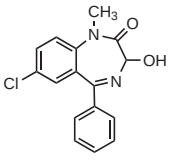

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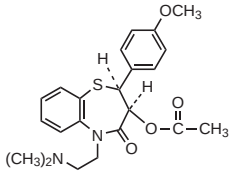
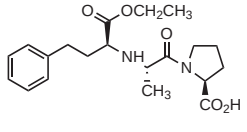


Diltiazem



Enalapril

1. Conduct a thorough and mechanistic SAR analysis of the three therapeutic options in the case.
2. Apply the chemical understanding gained from the SAR analysis to this patient's specific needs to make a therapeutic recommendation.

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