The Pharmacology and Mechanism of Action of Zolpidem

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INTRODUCTION

Each of us spends approximately one third of our life sleeping. Thanks to technological advances in methods of evaluating the electrical activity of the brain during sleep and wakefulness (polysomnography) we now know a great deal about the physiology of sleep in humans and lower animals. We know less about the functions of sleep, however, although there has never been any shortage of theory and speculation on this topic. The biological significance of sleep is emphasized by the important effects of sleep disturbances. Sleep disorders are classified by the DSM IV into dyssomnias and parasomnias; the major clinical problem in this area is probably primary insomnia.

Insomnia is not itself a disease and may or may not be considered a symptom of another physical or psychiatric disorder. It is best characterized as a complaint of difficulty in initiating or maintaining sleep or of sleep which is not satisfying or restorative. It is essentially a subjective problem, therefore, although polysomnographic and other objective methods may have important roles to play in evaluating the significance of the problem and the effectiveness of treatments. Assessments of the prevalence of insomnia vary, but all recent surveys indicate that it is a common problem. Ohayon (55), using a telephone interviewing technique of a representative sample of the French population, reported that 18.6% of the sample complained of insomnia. This figure is, in fact, slightly lower than those obtained in other populations (some surveys have reported that up to 40% of the population may suffer from insomnia in a given year) (14,29,39,49). Marked differences between different countries have also been reported (90). Complaints of insomnia increase with age and are more common in women than in men (61,88). Using a figure for the prevalence rate of insomnia in the population of the United States of 32 to 33%, Stoller calculated that the economic costs associated with this disorder could be approximately $100 billion (83). Although such calculations are necessarily estimates and subject to controversy, it has also been proposed that the annual cost of accidents alone in the USA associated with insomnia may be about $50 billion (45,96).
Much insomnia is associated with disturbances in patterns of living or disruptive life events and is, therefore, transitory and may not require specific treatment. In other patients the problem may be solved by changes in behavior or lifestyle, usually referred to as good sleep hygiene (35). For example, patients should be advised to maintain regular sleeping times, avoid stimulants such as coffee in the evenings and so on (50). For patients in whom insomnia is a more intractable problem, however, treatment with hypnotic drugs may be appropriate. Indeed, a significant number of people report that they self-medicate with alcohol, herbal drinks, or over-the-counter sleep aids to assist sleep (16).

Over the last century, a variety of hypnotic agents have been introduced into medicine ranging from the bromides and chloral hydrate through the barbiturates and the benzodiazepines to the newer non-benzodiazepine agents. Although not even the newer agents probably achieve all the criteria of the “ideal” hypnotic as defined by Bartholini (6), progress has certainly been made in inducing and maintaining sleep while limiting unwanted effects. Many brain mechanisms are undoubtedly involved in the regulation of sleep but it is remarkable that the great majority of drugs used for sleep induction act by potentiating the actions of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). The present paper will summarize the pharmacology of the non-benzodiazepine hypnotic, zolpidem, and its interaction with GABA_A receptors in the central nervous system.

**CHEMISTRY**

Zolpidem \((N,N,6\text{-trimethyl-2[4-methyl-phenyl]}\text{imidazo[1,2-a]pyridine-3-acetamide hemitartrate})\) is a stable, water-soluble, microcrystalline solid with a molecular weight of 392.4 (weight of salt). Its structural formula is shown in Fig. 1 in comparison with two other non-benzodiazepines, zopiclone, which is also used in the treatment of insomnia (54) and zaleplon which is in clinical development also as a hypnotic (8). The medicinal chemistry program that led to the discovery of zolpidem and other imidazopyridine derivatives has been described by George et al. (34).

**PRECLINICAL PHARMACOLOGY**

The aim of the drug discovery program that led to zolpidem was to identify a non-benzodiazepine compound that would show a rapid-onset, short-duration hypnotic effect and would bind to benzodiazepine (BZ) receptors. Zolpidem has these characteristics (24), but during the course of the pharmacological evaluation of the compound it was found that both, its pharmacological profile and its mechanism of action, differed in potentially significant ways from those of the benzodiazepines themselves.

Since the objective of the research program was to synthesize and develop ligands for BZ receptors, the first level of primary screening necessarily involved a receptor-binding assay. Many imidazopyridine derivatives were found to have high and selective affinities for these sites, zolpidem displacing radiolabelled diazepam from preparations of rat brain membranes with affinities of 27 nM in the cerebellum and 109 nM in the hippocampus (4). These in vitro studies were followed by investigation of the effects of zolpidem on the...
EEG of rats and cats; it was found that the compound produced a rapid-onset, short-duration hypnotic effect (4,24).

Electrocorticographic (ECoG) measures in immobilized rats showed that zolpidem at doses of 0.1 to 1.0 mg/kg by the intraperitoneal route, and doses approximately three times higher when administered orally, produced a pattern of activity characterized by slow waves (2 to 4 Hz) with only transient periods of fast activity (12 to 14 Hz) at high doses (21,24). This was considered to be of particular interest because, in similar experiments, benzodiazepines were typically observed to produce a greater degree of fast activity which was thought not to correspond to a pattern of normal sleep (24). The hypnotic effect of zolpidem, consisting of an increase in slow-wave or non-rapid eye movement (NREM) sleep was confirmed with measures of the EEG in freely moving rats and cats. In these studies, zolpidem produced a short-duration (~3 h in rats, depending on dose) increase in NREM sleep with little effect on the proportion of REM sleep except at high doses (21,24,26).

Fig. 1. Structural formula of the imidazopyridine hypnotic zolpidem in comparison with those of two other non-benzodiazepine hypnotics, zopiclone and zaleplon.
Recently, the analysis of the microstructural elements of sleep provided a novel approach to the evaluation of the stability and quality of sleep. It is possible to model insomnia in rats using a variety of methods, such as recording during the dark phase of the nocturnal cycle, depleting brain serotonin, or making lesions of certain brain regions such as the olfactory bulbs. Using such techniques, it has been found that sleep patterns show numerous periods of wakefulness and light sleep indicating poor sleep quality. In such experiments, zolpidem reduced sleep fragmentation and microarousals and induced a more stable overall pattern of sleep (22,23).

Behavioral Effects

The effects of zolpidem as measured by EEG were confirmed with behavioral experiments in rats and mice which showed decreases in locomotor activity and other unconditioned and conditioned behaviors (24,56,74). Like other compounds acting as agonists at BZ receptors, zolpidem produced a variety of other behavioral and neuropharmacological effects. These included anticonvulsant actions, motor incoordination, discriminative stimulus properties, anxiolytic-like effects, and actions on learning and memory. When the potency of the drug to induce these different actions was analyzed in detail, however, zolpidem showed an unexpected profile.

One of the pharmacological tests most sensitive to benzodiazepines is convulsions induced in rats or mice by pentylenetetrazol; this test has been used as a screening procedure for this type of drug. Zolpidem was found to antagonize pentylenetetrazol-induced seizures in mice at doses similar to those that blocked seizures produced by electroshock and higher than doses that reduced locomotor activity, a presumed reflection of the drug’s sedative effect (56). These results are shown in Fig. 2, which emphasizes the difference between the pattern of results obtained with zolpidem and those of quazepam, brotizotam, and zopiclone.

These findings were important since they indicate that in mice, as in rats (7,74), sedative effects seem to predominate over other actions of zolpidem (24). It is also of particular interest that increases in muscle relaxation and motor incoordination (which are not particularly desirable in a hypnotic drug) occurred only at the highest doses. These findings are also of considerable theoretical interest, however. It had previously been assumed that all the pharmacological effects of benzodiazepines were mediated by activity at similar receptors, possibly situated in different regions of the CNS. The observation that different dose ranges of any particular benzodiazepine were necessary to give rise to different effects was believed to be related to receptor reserve or the proportion of receptors that needed to be occupied to produce each effect. Thus, occupation of a relatively small number of receptors was sufficient to block pentylenetetrazol-induced seizures, whereas many more receptors would have to be occupied before sedation occurred (cf. brotizolam in Fig. 2). Of course, the observation of a profile such as that of zolpidem indicates that this hypothesis cannot be correct and such findings are more consistent with the idea that different effects of BZ-receptor agonists might be mediated by different receptor subtypes (69,101). The extent to which biochemical and electrophysiological results with zolpidem are consistent with this hypothesis is considered below.

Zolpidem has also been studied in a variety of other behavioral procedures and results generally show that sedative effects predominate and may mask other actions. The drug
Fig. 2. Dose-related pharmacological effects of zolpidem, quazepam, brotizolam, and zopiclone in mice. Measures are: exploratory locomotor activity (EA), inhibition of seizures induced by pentylenetetrazol (PTZ) and electroshock (MES), muscle relaxation as assessed by the hanging grid test (MYO), and ataxia as measured by a rotarod test (ATA). From ref. 56.
has anxiolytic-like effects but only in a limited range of tests and only at doses that decrease behavioral output (24,36,53,69). Similarly, increases in food and fluid intake in rodents, which are consistently reported with benzodiazepines, have been reported only rarely with zolpidem (15,18,56,74,81,100). An effect on the learning of an avoidance response was also found in mice only at sedative doses (71).

Like many psychotropic agents, agonists at BZ receptors can serve as discriminative stimuli and drug discrimination methods have been extensively used to characterize the behavioral pharmacology of zolpidem. In rats there is only limited cross-substitution between zolpidem and benzodiazepines (24,71) and these findings have been used to develop theories concerned with the role of receptor subtypes (69,70). The few studies that have been carried out in this area with non-human primates suggest, however, that differences between zolpidem and benzodiazepines may be less apparent in these species (37,65). In a recent drug discrimination experiment using human volunteers, the subjects were able to learn a discrimination between zolpidem and triazolam (51).

**Effects of Repeated Administration**

Chronic administration of benzodiazepines, particularly at high doses, can lead to a decrease in drug efficacy or potency (pharmacological tolerance) or the appearance of withdrawal or abstinence signs when drug treatment terminates (physiological dependence). The extent to which these phenomena occur under conditions of normal clinical use is of course a cause of concern for both physicians and patients and there is evidence that physiological dependence does develop in the clinic with at least some benzodiazepines (99).

It is imperative, therefore, that, during the development of novel hypnotic or anxiolytic drugs, studies are carried out to investigate the conditions under which tolerance or dependence may occur. A number of experiments have been described involving repeated administration of zolpidem to rats and mice and the results suggest that little pharmacological tolerance develops to the anticonvulsant or sedative effects of the drug (21,57,73,75,77). Of particular interest is the finding that, when zolpidem was compared with equivalent doses of other BZ-receptor agonists, marked differences were observed between the different drugs. Fig. 3 shows that, while tolerance developed quite rapidly to the depression of conditioned behavior produced by midazolam, little tolerance occurred with equivalent doses of zolpidem (75). In contrast to these rodent experiments, a study involving repeated administration of zolpidem to baboons showed apparent tolerance to the ataxia produced by the drug occurring within a few days (37).

The development of pharmacological tolerance is presumably due to the entrainment of compensatory physiological mechanisms during chronic drug treatment and similar processes may underlie physiological dependence. It is not surprising, therefore, that several experiments with mice have reported that little spontaneous or precipitated withdrawal is observed following repeated administration of zolpidem (57,93). Similarly, in a study involving squirrel monkeys, it was found that fewer signs of precipitated withdrawal occurred with zolpidem than with diazepam (64). However, precipitated withdrawal from zolpidem was reported when very high doses were given to mice (300 mg/kg/d) (84) and several studies have reported withdrawal signs classified as mild or intermediate in zolpidem-treated baboons (37,97,98). It is likely, however, that the doses of zolpidem used
in these primate studies may have produced levels of receptor occupation much higher than those ever likely to occur under normal clinical conditions (9, 76).

This set of studies indicates that even at sedative doses of zolpidem little tolerance or physiological dependence develops, at least in rodents. At high doses these phenomena are more likely to occur, as would be expected, and there may also be significant differences among different species of laboratory animals. This research appears to provide a good prediction of the clinical situation. Tolerance and dependence appear not to have been reported during the normal clinical use of zolpidem at recommended doses, although there are a very small number of reports that suggest tolerance and/or dependence involving abnormally high doses (see refs. 17, 66, 82 for review).

MECHANISM OF ACTION

Binding to Native Receptors

As noted in an earlier section, zolpidem was originally selected for investigation and ultimately clinical development because it was found to displace radiolabelled
benzodiazepines from their binding sites in the CNS. In addition, the pharmacological effects of zolpidem are blocked by the BZ-receptor antagonist flumazenil (24,68), showing that the drug exerts its actions through these sites. However, it soon became apparent that, as described in the preceding sections, the pharmacological effects of zolpidem after acute and repeated administration showed certain interesting differences from those of benzodiazepines. Zolpidem’s mechanism of action was, therefore, investigated in greater detail. This was done using receptor-binding methods and several laboratories showed a more selective binding profile of zolpidem than that observed with the benzodiazepines themselves.

Zolpidem displaced the binding of different benzodiazepines from brain membrane preparations or brain sections in a regionally selective way (4,11,20,48,79). In particular, zolpidem displaced benzodiazepines more potently in the cerebellum than in the hippocampus or the spinal cord, a pattern previously defined as selectivity for Type-1 or BZ\textsubscript{1} receptors (80). (Some authors have proposed that the nomenclature $\omega$ should be used in place of BZ — and therefore $\omega_1$ and $\omega_2$ in place of BZ\textsubscript{1} and BZ\textsubscript{2} — because many of the drugs that bind to these sites do not have benzodiazepine structures. The receptors will, therefore, be referred to as BZ($\omega$) for the remainder of the paper [43]). The appropriate nomenclature for these sites has recently been discussed in detail (5). Table 1 provides several examples of the BZ\textsubscript{1}($\omega_1$) selectivity of zolpidem.

Studies involving the binding of labeled zolpidem itself also observed a more limited and heterogeneous distribution of binding sites in the rat CNS than that found with benzodiazepines (3,48). Autoradiographic studies with [\textsuperscript{3}H]zolpidem in sections of

*Table 1. Examples of the regional selectivity of binding of zolpidem to BZ($\omega$) receptors in rat brain membrane preparations in vitro*
monkey and human brain showed that zolpidem binds with greater regional selectivity than do benzodiazepines (20), although a recent study found that the patterns of selectivity were not identical in rats and monkeys (25, but see also 76).

The binding of zolpidem to BZ(\(\omega\)) receptors in different regions of the CNS has also been investigated \textit{in vivo} in rodents sacrificed after systemic administration of drug and labeled ligand (10,11) and in baboons and humans using positron emission tomography (1,76). In the animal studies, the regional selectivity of zolpidem’s binding was again apparent (Table 2). However, the PET study in human volunteers found similar levels of receptor occupation in different brain regions (mean of 29%) after administration of zolpidem 20 mg. This is likely to be related to the CNS areas chosen for investigation and because the proportion of sites occupied was relatively low. On the basis of these results it has been calculated that the clinical dose of zolpidem 10 mg would be expected to occupy only 10 to 15% of the total population of BZ(\(\omega\)) sites, a proportion considerably less than that seen with pharmacologically equivalent doses of benzodiazepines (9).

**Activity at Recombinant GABA\(_A\) Receptors**

It has been known for some time that BZ(\(\omega\)) binding sites are associated with the GABA\(_A\) subtype of receptors for the inhibitory neurotransmitter GABA. Recent developments in molecular biology have shown that GABA\(_A\) receptors, like other receptors of the ligand-gated ion-channel family, are made up of five subunits that occur in several families of polypeptides (\(\alpha\), \(\beta\), \(\gamma\), etc.) (47,52). The BZ(\(\omega\)) binding sites are associated with the \(\alpha\) and \(\gamma\) subunits and functional recombinant GABA\(_A\) receptors can be expressed in, for example, human embryonic kidney (HEK) cells by combining \(\alpha\), \(\beta\), and \(\gamma\) subunits. Such preparations can then be used in biochemical and electrophysiological experiments to investigate the mode of action of different pharmacological agents (78).

Seeburg et al. (62) first reported that GABA\(_A\) receptors consisting of an \(\alpha_1\) subunit in combination with \(\beta_2\) and \(\gamma_2\) subunits showed high affinity for zolpidem, whereas receptors

TABLE 2. Regional selectivity of displacement by zolpidem of \(^3\text{H}\)flumazenil binding in the rat CNS in vivo

<table>
<thead>
<tr>
<th>Region</th>
<th>Selectivity (%)</th>
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<tbody>
<tr>
<td>Cortex</td>
<td>28</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>29</td>
</tr>
<tr>
<td>Striatum</td>
<td>30</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>27</td>
</tr>
</tbody>
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\[\text{CNS Drug Reviews, Vol. 4, No. 4, 1998}\]
with $\alpha_2$ or $\alpha_3$ subunits showed much lower affinity, and receptors containing $\alpha_5$ subunits showed no affinity at all (Table 3). These results indicated that GABA$_{\alpha}$ receptors containing $\alpha_1$ subunits correspond to the pharmacologically defined BZ$_1(\omega_1)$ receptor whereas the BZ$_2(\omega_2)$ sites are probably heterogeneous, corresponding to GABA$_{\alpha}$ receptors containing $\alpha_2$, $\alpha_3$, or $\alpha_5$ subunits. The selectivity of zolpidem has been confirmed in a number of subsequent studies which have also shown that, in contrast, most other BZ(\omega) site agonists bind to GABA$_{\alpha}$ receptor subtypes with similar affinities (13,28,38).

That these differences in affinity between different GABA$_{\alpha}$ receptor subunit combinations have functional significance has been shown using single-cell electrophysiological recordings. When zolpidem is applied to receptors containing $\alpha_1$ subunits, low concentrations potentiate the effect of GABA whereas higher concentrations are required in receptors containing $\alpha_2$ or $\alpha_3$ subunits and there is little or no response in $\alpha_5$-containing receptors (12,63,94). These findings are illustrated in Fig. 4, which also shows the lack of selectivity of diazepam.

**PHARMACOKINETICS AND METABOLISM**

The pharmacokinetic and metabolic profiles of zolpidem have been investigated in detail in experimental animals and humans and several descriptions of this information are available (30,33,67). After oral administration, zolpidem is rapidly and completely absorbed with bioavailabilities of 20% in the rat, < 10% in monkeys and 70% in humans. Peak plasma levels are reached after approximately 15 min in rats, 30 min in monkeys, and 1 h in humans. Elimination half-lives are of the order of 1.5 h in rats, 1 to 2 h in monkeys and 1.5 to 3.0 h in humans. The drug rapidly crosses the blood-brain barrier.

Zolpidem metabolites have been identified and pharmacologically inactive (33). The major metabolite is a carboxylic-acid derivative that accounts for > 50% of the administered drug. In humans, biotransformation by cytochrome P450 (CYP) isoenzymes involves mainly CYP-3A4, although CYP-1A2 and CYP-2D6 also play minor roles (58). Experimental studies indicate that the risk of pharmacokinetic drug interactions in clinical practice is low (30,67) although co-administration with inducers of CYP enzymes may result in reduced plasma concentrations and decreased effectiveness of zolpidem (91).

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**TABLE 3. Displacement of [$^3$H]flumazenil binding from recombinant GABA$_{\alpha}$ receptors with different subunit combinations**

<table>
<thead>
<tr>
<th>Subunit Combination</th>
<th>Affinity</th>
</tr>
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<tbody>
<tr>
<td>$\alpha_1$</td>
<td>High</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Moderate</td>
</tr>
<tr>
<td>$\alpha_3$</td>
<td>Moderate</td>
</tr>
<tr>
<td>$\alpha_5$</td>
<td>No Affinity</td>
</tr>
</tbody>
</table>

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CLINICAL EXPERIENCE WITH ZOLPIDEM

Efficacy

Zolpidem was first introduced to the market as a short-term treatment for insomnia in France in 1988. It has subsequently been registered in > 70 countries. It was first marketed

Fig. 4. Potentiation by diazepam and zolpidem of the GABA-induced Cl⁻ current in cell lines transfected with GABAₐ receptors containing α₁ (●), α₃ (▲), or α₅ (■) subunits. Results are shown as the potentiation of the maximum GABA-induced current in each cell line. Similar concentrations of diazepam were effective in the three cell lines, whereas zolpidem showed selectivity of action at GABAₐ receptors containing α₁ subunits. From ref. 12.
in the United States in 1993. In some countries, zolpidem is the most widely prescribed and used hypnotic drug.

A large number of clinical studies of the efficacy of zolpidem in inducing and maintaining sleep, involving tens of thousands of patients, have been carried out and the results have been published. Several detailed reviews of this literature are available (44,59,95). Zolpidem's activity has been evaluated using subjective assessments in which patients responded to questionnaires concerning the latency, quality, and duration of their sleep. In such studies, zolpidem was reported to reduce sleep latency, increase duration, and produce more satisfying sleep. These findings have been confirmed in trials using objective polysomnographic methods in which sleep latency and nocturnal awakenings were reduced and sleep duration was increased. These studies have also reported that sleep architecture was not disrupted during a night of zolpidem-assisted sleep (95).

Analyses of the microstructure of sleep have also been carried out using measures of the cyclic alternating pattern (CAP). CAP rate is significantly correlated with the subjective appreciation of sleep quality even in the absence of significant macrostructural alterations (87). Zolpidem was found to reduce the increased CAP rate shown in the disturbed sleep of insomniac patients and to attenuate the instability of the sleep patterns produced by noise (85,86).

In seeking to develop zolpidem as a rapid-onset, short-duration hypnotic, a major aim was to identify a drug that would not give rise to impairments in performance the day after a night of drug-assisted sleep. Such next-day effects have been a significant cause for concern with some hypnotic barbiturates and benzodiazepines. A number of studies were therefore carried out to investigate next-day alertness and psychomotor performance with zolpidem (for review see refs. 19,89). The results of these studies showed that when appropriate doses of zolpidem (5 to 10 mg) were taken at bedtime there were minimal effects on cognitive or psychomotor performance or daytime drowsiness the next morning.

Safety

Before registration and marketing, zolpidem was tested in the appropriate toxicological screens in experimental animals. The results showed that the compound was extremely well tolerated with a large therapeutic ratio (31). In the clinic, controlled trials and post-marketing surveillance have confirmed the positive safety profile (2,17,60). Zolpidem is also safe in overdose; Garnier et al. (32) reported in a review of 344 cases of intentional, acute overdose that the effects were generally benign, requiring no specific measures except support and perhaps gastric lavage. In post-marketing surveys most reported adverse events were CNS related and not unexpected for a hypnotic drug (e.g., drowsiness or sedation). Gastrointestinal events such as nausea are also reported occasionally, particularly at higher doses (60). It has been suggested, in fact, that such effects may limit the abuse potential of zolpidem (27). Rebound insomnia following cessation of a course of hypnotic treatment, which has been reported to be a problem with some other drugs in this class, is also of minimal significance when zolpidem is used at the correct doses and for an appropriate duration (92).
DISCUSSION

In the 10 years since it was first introduced to the market, zolpidem has become a widely used and successful hypnotic drug. When taken according to prescribing guidelines it is a very effective and safe medicine. Zolpidem has also become an important experimental tool for both laboratory workers interested in the neuropharmacology and behavioral pharmacology of hypnotic drugs and researchers studying the structure and function of GABA_A receptors. The selectivity of zolpidem for different GABA_A-receptor subtypes, particularly its lack of activity at receptors containing α5 subunits, makes it an important chemical tool for research on the significance of GABA_A-receptor heterogeneity. Until more selective compounds are described, zolpidem is likely to remain a very important drug for laboratory research.

The clinical profile of zolpidem also has a number of characteristics highly desirable in an agent used for the short-term treatment of insomnia. The extent to which the reported differences in human experimental pharmacology and clinical actions show that zolpidem has major clinical advantages over some other short-acting hypnotics, such as triazolam, remains a matter for debate (40,42,46). The more selective pharmacological profile and mechanism of action of zolpidem, however, suggest that, at least from a theoretical point of view, it might offer potential advantages over other hypnotics. As summarized above, zolpidem acts selectively at certain subtypes of GABA_A receptors, where it may also show a higher intrinsic efficacy than other agents (41). These characteristics mean that clinically active doses of zolpidem would be expected to occupy a smaller proportion of the total population of BZ(α) sites associated with GABA_A receptors than other drugs, as positron emission tomography (PET) studies in humans seem to confirm (9). Since zolpidem is clearly an effective agent in inducing sleep, the drug’s pharmacology would indicate that this action is likely to involve GABA_A receptors containing α1 subunits and that the additional sites acted on by non-selective drugs are unnecessary for this effect. However, occupation of additional receptors might have significance for unwanted pharmacological effects or for the development of pharmacological tolerance or physiological dependence (102). The good safety profile of zolpidem (17) may, therefore, be related to the drug’s more selective mechanism of action.

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