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Efficacy of Hypnotic Medications and Other Medications Used for Insomnia

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Insomnia is one of the most common sleep disorders in the United States and other Western countries, with prevalence estimates ranging between 10% and 15% of the adult population; up to one third of all adults report insomnia symptoms in a given year [1]. The socioeconomic impact of this disease is tremendous. The direct cost of insomnia (the cost of treatment) has been estimated to be between 10 and 15 billion dollars per year based on reports published in the early to mid-1990s [2,3]. That estimate does not include the costs attributable to increased absenteeism and property damage caused by accidents [4]. The human cost in terms of medical comorbidities, suffering, and reduced quality of life is not so easily quantified.

The mainstay of medical treatment for insomnia for the last 80 years has been pharmacotherapy, beginning with barbiturates in the early 1900s. Barbiturates and similar sedative and anesthetic agents were used until the 1960s and 1970s, when benzodiazepines, with markedly reduced risk of abuse, dependence, tolerance, and respiratory depression, became available. The classes of drugs now commonly used for insomnia include

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benzodiazepine receptor agonists (BzRAs; benzodiazepines and nonbenzodiazepines), a melatonin receptor agonist, antidepressants, and a handful of miscellaneous agents including antipsychotics, antihistamines, and muscle relaxants. Currently the Food and Drug Administration (FDA) has approved 10 medications for use in insomnia (Table 1), but a wide variety of other medications is often used despite lack of established efficacy and risk for dangerous side effects. The 2005 National Institutes of Health State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia in Adults was organized in part to review the scientific evidence regarding the efficacy and effectiveness of pharmacotherapy for adults who have chronic insomnia. The review panel concluded that evidence is available to support only the use of BzRAs for the pharmacological treatment of insomnia [5].

Hypnotic efficacy studies use one or more measures of sleep including patient reports, physician/observer ratings, polysomnography (PSG), and, in rare cases, actigraphy. Patient-report measurements are varied and often include quantitative estimates of sleep duration, time to sleep onset, or the number of awakenings during the night. Assessments of sleep quality are also frequently made. Global impression measures often combine multiple facets of sleep quality and quantity into a single question, which may be more susceptible to patient interpretation but is relevant to the clinical situation and typically correlates well with objective measures such as the time to fall asleep and total sleep duration [6]. Global impression questions are the most common type of physician/observer ratings. Typical PSG efficacy variables include latency to the onset of persistent sleep (LPS), the standard PSG measure of sleep induction, and sleep maintenance measures such as wake time after sleep onset (WASO) and number of awakenings. Measures combining both sleep induction and maintenance include total sleep time (TST) and sleep efficiency, the ratio of TST to time in bed. PSG also allows identification of the time spent in various sleep stages, the number of stage shifts or microarousals, and the time awake during different segments of the night (eg, during each quarter of the night). Actigraphy measures movement or inactivity of a limb, which, in conjunction with sleep diary information, allows an estimate of sleep latency and TST. More recently, consideration has been given to improving the waking symptoms of insomnia as well as the sleep symptom. Only a few investigations have systematically included ratings of waking function as additional efficacy variables. These ratings include questions about daytime mood, alertness, or ability to function, generally assessed using Likert scales or, infrequently, using standardized tools

Table 1: **Selected drugs used for insomnia in the United States**

FDA-approved hypnotics			Drugs commonly used off-label			OTC medications
Benzodiazepines	*Other benzodiazepine receptor agonists*	*Melatonin receptor agonist*	*Benzodiazepines*	*Antidepressants*	*Antipsychotics*	*Miscellaneous*
Triazolam	Zaleplon	Ramelteon	Lorazepam	Trazodone	Olanzapine	Valerian
Temazepam	Zolpidem		Alprazolam	Mirtazapine	Quitiepine	Melatonin
Estazolam	Zolpidem CR		Clonazepam	Doxepin		Alcohol
Flurazepam	Eszopiclone			Amitriptyline		Diphenhydramine
Quazepam						Cyclobenzaprine
						Hydroxyzine

These constitute the most commonly used agents for the management of insomnia in the United States, either by prescription or over the counter (OTC). Among those drugs with a Food and Drug Administration (FDA) indication for insomnia, flurazepam and quazepam are not often used because of their long duration of action and predisposition to residual sedation. Among the drugs without an FDA indication for management of insomnia, doxepin and amitriptyline are less commonly used for their sedating effect, in comparison to the other sedating antidepressants listed.

such as the Profile of Mood States or the Epworth Sleepiness Scale.

Most hypnotic efficacy studies involve primary insomniacs, excluding patients who have insomnia with significant comorbid medical or psychiatric conditions or circadian-based insomnia. Assessing the insomnia-specific effects of hypnotics, independent of ancillary effects (eg, anxiolysis), is the logic behind this approach. Comorbid insomnia (ie, insomnia coexisting with other medical, psychiatric, or sleep disorders), however, is more common than primary insomnia [7]. Fortunately, limited published research indicates that hypnotic efficacy does not seem to be altered by comorbid conditions, suggesting that the results of studies in primary insomnia can be generalized to other forms of insomnia.

The benzodiazepine receptor agonists

Of all of the drugs used for the treatment of insomnia, the BzRAs have been most rigorously investigated. BzRAs fall into two groups, those with a benzodiazepine molecular structure, such as triazolam or temazepam, and those with other chemical structures, such as zolpidem or eszopiclone. The hypnotic effect of these agents is mediated by their action at the gamma-aminobutyric acid-type A ($GABA_A$) receptor-channel complex, a five-protein transmembrane channel that functions as a gated passage for chloride ions. GABA is the major inhibitory neurotransmitter of the brain, and the activity of the $GABA_A$ ion channel is affected by a number of chemical ligands including BzRAs, alcohol, neurosteroids, and barbiturates that act at different receptor sites on the complex. BzRAs influence the channel's behavior and, as a consequence, modulate the influx of chloride ions into the neuron only when the channel is activated by GABA. BzRAs bind to one or more subtypes of benzodiazepine receptors. Benzodiazepines are relatively nonselective with similar binding affinities for several receptor subtypes. Some nonbenzodiazepine BzRAs have a more selective profile, binding preferentially to $GABA_A$ receptor complexes containing $\alpha 1$ subunits. In point-mutation knockin studies, different $GABA_A$ receptor subtypes seem to mediate different pharmacologic effects, with the $\alpha 1$ subtype described as influencing sedation, amnesia, and anticonvulsant properties. This effect has led to the suggestion that the selectively binding BzRAs may produce a more specifically hypnotic effect than nonselective BzRAs, but, no substantive difference attributable to binding specificity has yet been demonstrated in clinical studies (Table 2).

Efficacy

All of the BzRA hypnotics have been shown to be efficacious for the treatment of insomnia, although there are some differences among these drugs because of variations in rapidity of onset and duration of hypnotic action. Their efficacy has been measured both by PSG studies and patient reports in sleep diaries and questionnaires [5]. Meta-analyses of the BzRAs have supported their hypnotic efficacy based on both patient reports and PSG measures, at least over a short treatment period [8,9]. In one

Table 2: **Selected pharmacokinetic characteristics of FDA-approved benzodiazepine receptor agonist hypnotics**

Drug	Time to maximal plasma concentration (minutes)	Elimination half life (hours)	Major metabolic pathway	Recommended doses (mg)	
				Adult	*Elderly*
Zaleplon	60	1	Aldehyde oxidation	10	5
Zolpidem	90	1.5–2.4	CYP_{450} oxidation	10	5
Zolpidem[a]			CYP_{450} oxidation	12.5	6.25
Triazolam	60–120	2–6	CYP_{450} oxidation	0.25	0.125
Eszopiclone	60	5–7	CYP_{450} oxidation	2–3	1–2
Temazepam	variable	8–20	Glucuronidation	30	15
Estazolam	30–360	8–24	CYP_{450} oxidation	2	1
Flurazepam	30–60	48–120[b]	CYP_{450} oxidation	30	15
Quazepam	90	48–120	CYP_{450} oxidation	7.5–15	7.5–15

The time required for an individual agent to reach its maximal serum concentration ($t_{max,}$) is a measure of its rate of absorption and the time to onset of any sleep promoting effects. The half-life is a measure of elimination, providing a relative estimate of how long sleep-promoting effects might last.

Abbreviation: $CYP_{450,}$ cytochrome P450.

[a] Because of a formulation which produces biphasic absorption characteristics, time to maximal plasma concentration and elimination half-life do not adequately reflect the pharmacokinetic profile.

[b] The active metabolite of desalkyl-flurazepam.

meta-analysis, for example, the median period of treatment for a typical individual trial was approximately 1 week. Because these meta-analyses combine studies of various agents at multiple doses, they are helpful in describing general effects of these medications but are less helpful in guiding specific treatment decisions.

All of the BzRA hypnotics reduce sleep latency, attributable to rapid absorption and onset of hypnotic activity. Investigations assessing maintenance of sleep typically find that a drug is more likely to be efficacious in maintaining sleep as its duration of action lengthens. Within this class, elimination half-life and dose are the primary determinants of duration of hypnotic action. Most of the BzRAs also increase TST. The exception is zaleplon, which does not reliably increase TST. Zaleplon's short duration of action, however, allows administration during the middle of the night with minimal risk of residual sleepiness after rise time, provided 5 hours of sleeping time remains at the time of administration [10]. A new extended-release formulation of zolpidem containing both an immediate release and a delayed-release portion has recently become available. Little efficacy data have yet been published. Indiplon, another BzRA having immediate-release and extended-release formulations is currently pending FDA review.

Longer-duration efficacy trials suggest continued hypnotic benefit of BzRAs. In the early 1980s, Oswald and colleagues [11] reported on two benzodiazepines that retained their effect on some qualitative patient estimates of hypnotic efficacy over 5 to 6 months of use. More recent studies of zolpidem and zaleplon used PSG measures to show persistent efficacy over 5 weeks of nightly use [12,13]. A large and recent study of more than 500 primary insomniacs taking eszopiclone (3 mg) nightly over 6 months demonstrated persistent reductions in both subjective sleep latency and WASO when compared with placebo [14]. The amount of TST, number of awakenings, and quality of sleep also were better than with placebo at each time point. In an open-label 6-month extension of this trial, the subjects receiving eszopiclone (3 mg) continued to show significant improvements in latency to sleep onset and WASO, and an improved daytime sense of well-being and ability to function, when compared with their original baseline before the double-blinded phase and when compared with the time of entry into the open-label phase [15]. Preliminary reports indicate that other BzRAs also demonstrate sustained efficacy with nightly use for a few months or more. Tolerance often is cited as a potential concern when hypnotic medications are administered nightly beyond a short period of time [16], but tolerance to the hypnotic effects of BzRAs has not developed in most studies of hypnotic efficacy, most of which have been 4 to 12 weeks in duration, or in the few examining 3 to 6 months of nightly use.

Non-nightly hypnotic administration has also been studied. Zolpidem (10 mg) given on a non-nightly schedule for up to 12 weeks improved patient reports of sleep latency, number of awakenings, TST, and sleep quality, when compared with placebo [17,18]. No rebound insomnia was seen on nights medication was not taken, and biweekly investigator global ratings of insomnia showed a reduction in severity even when treatment and non-treatment nights were considered as a whole.

Studies of the effectiveness of BzRAs have not been conducted in clinical populations. Some information regarding effectiveness can be inferred from patient surveys or unblinded open-label protocols. In a large study of 532 patients surveyed by Ohayon and colleagues [19], 66.5% reported "a lot" of improvement in sleep quality, whereas only 14.4% reported little or no improvement with the use of prescription hypnotics. In another survey relying on telephone interviews, there was a high rate of satisfaction with the effect hypnotic medications had on sleep in individuals who had a history of either significant trouble with insomnia or use of a medication for sleep [20]. This second survey study balanced the positive effects of the hypnotics with their negative effects by asking the respondents, "Taking into account both the positive effects on your sleep and daytime functioning and any negative effects you may have experienced, would you take this medication again for the same purpose?" Of those who responded, 84% of those taking triazolam and 74% of those taking temazepam indicated they would continue to use these hypnotics.

A small number of efficacy studies suggest that the efficacy of BsRAs in chronic comorbid insomnia is essentially equivalent to their efficacy in primary insomnia. For example, postmenopausal women reported considerable improvements in sleep latency, TST, WASO, and global impression of sleep quality over 4 weeks of treatment with zolpidem (10 mg) [21]. Similarly, Asnis and colleagues [22] found that the response to zolpidem (10 mg) on patients who have major depression under treatment with a selective serotonin reuptake inhibitor and who continue to have significant insomnia is similar to the response in patients who have primary insomnia. Eszopiclone has also been shown to be efficacious for insomnia coexisting with major depression [23].

Melatonin receptor ligands

Two substances that act at melatonin receptors are currently used to promote sleep: melatonin and

ramelteon. Melatonin, a pineal hormone that is available as a health aid, is involved in circadian system regulation, among other potential biologic functions [24]. Ramelteon is a synthetic melatonin receptor agonist that was approved by the FDA in 2005. Three melatonin receptors, MT1, MT2, and MT3, have been identified, with wide distribution throughout the body and brain. The sleep-promoting effect of melatonin and ramelteon is probably mediated by MT1 and MT2, although melatonin does bind to intracellular proteins and nuclear receptors as well [25]. Melatonin does influence activity at some GABA receptors, but there is no evidence this activity produces significant hypnotic effects [26].

Efficacy

Ramelteon, a MT1 and MT2 agonist, is approved by the FDA with an indication for the treatment of insomnia characterized by difficulty with sleep onset. The limited indication (ie, only sleep-onset difficulty) reflects the repeated observation that ramelteon reduces sleep latency but does not impact sleep maintenance. Ramelteon is the only hypnotic that is not a Drug Enforcement Agency–scheduled substance, consistent with an absence of reinforcing and drug-liking properties in investigations of abuse liability [27].

Ramelteon (16 mg or 64 mg), when given to normal adults in a model of transient insomnia, improved LPS by 10 to 15 minutes, with a commensurate increase in TST [28]. There were no PSG differences between these doses, but patient reports indicated both shorter sleep latency and a longer TST for only the 16-mg dose. Similar improvements in sleep induction with short-term administration of ramelteon were demonstrated in primary insomniacs at doses between 4 and 32 mg [29] and elderly insomniacs at doses between 4 and 8 mg [30]. The dose effect was minimal, and there were no subjective improvements in sleep quality or TST. Improvement in sleep latency is maintained when nightly treatment is extended to 5 weeks for both adult [31] and elderly [32] primary insomniacs. In the majority of these studies, the improvement in TST typically is equivalent to the reduction in sleep latency. Patient reports reflect this objective improvement in sleep onset less consistently and typically indicate no effect on reported TST or sleep quality, also consistent with objective measures. The dose–response curve is remarkably flat, between 8 and 64 mg, for both PSG and patient-report variables.

Ramelteon has a time of maximal concentration of 0.5 to 1.5 hours and an elimination half-life of 1 to 2.6 hours. An active metabolite of reduced potency has a half-life of 2 to 5 hours. Because of the minimal effect on sleep maintenance despite these pharmacokinetic properties, and the tendency for subjective ratings to be less sensitive than PSG to improved sleep, ramelteon has been hypothesized to promote sleep through a nonsedating process. Ramelteon's sleep-promoting effect may be mediated by reducing the alerting output of the suprachiasmatic nucleus.

There are limited data indicating that exogenous melatonin has a hypnotic effect on insomniacs. In a study by Montes and colleagues [33], 10 primary insomniacs were given melatonin (0.3 mg), melatonin (1 mg), or placebo 1 hour before bedtime in a double-blind crossover design. No differences were seen between melatonin at these doses and placebo using PSG (sleep latency or TST) and subjective measures. There was a similar lack of improvement in sleep induction or maintenance measures or changes in daytime mood or alertness in 10 primary insomniacs administered 1 or 5 mg of melatonin, but they did report a subjective sense of improved sleep quality [34]. Subjects were not blind to treatment, however. Melatonin (5 mg) had no effect on either sleep parameters or daytime function in 15 subjects who had psychophysiologic insomnia studied using a crossover design in which the other arm was a placebo [35]. In a more recent study of individuals over the age of 50 years who developed chronic psychophysiologic insomnia after the age of 40 years, no improvements were seen in TST and sleep latency (PSG measures) with 0.1, 0.3, and 3 mg of melatonin 30 minutes before bedtime, but there were improvements in sleep efficiency during the mid-portion of the night at all dosages [36]. At a much higher dose of melatonin (75 mg), using a placebo crossover design, MacFarlane and colleagues [37] identified mild improvements in sleep-onset latency and daytime alertness in a double-blind study of 13 insomniacs; there were no improvements in sense of daytime well-being. In summary, melatonin in the range of dosages studied (0.1–5 mg), administered shortly before the typical bedtime, has no consistent effect on sleep or wake parameters in primary or psychophysiologic insomniacs.

In elderly primary insomniacs, in whom endogenous melatonin levels have been found to be lower than in other age groups, study results are mildly more promising but not conclusive. Administration of melatonin (2 mg fast release) 2 hours before bedtime did result in significant reductions in sleep latency but no change in sleep maintenance measures over a 7-day treatment period [38]. When a 2-mg slow-release formulation of melatonin was used instead, sleep latency and sleep duration were unchanged. This trial by Haimov and colleagues [38] also included a final 2-month period of treatment

with 1-mg slow-release melatonin to which only the patient was blinded. Significant improvements in both sleep latency and sleep efficiency were seen over this longer treatment period. The sleep measures in these three treatment conditions were, however, based on actigraphy, not PSG. There was no control group with which to make comparison in the final 2-month 1-mg treatment condition, so the change from baseline was not necessarily a treatment effect. Insomnia pharmacotherapy trials commonly lose some degree of significance in their outcome measures because of improvements in the sleep of the control groups [39]. In another double-blinded crossover trial by Garfinkel and colleagues [40], elderly insomniacs who had low melatonin levels and who were already taking benzodiazepines were given melatonin (2 mg slow release) in addition to their other medications. The treatment group improved significantly in WASO and sleep efficiency when compared with the control placebo arm, but in contrast to other melatonin trials improvements were also seen in TST and sleep latency. The sleep measures in this trial were also based on wrist actigraphy. This possible additive effect is interesting, but the results of this study do not support the use of melatonin alone as a hypnotic. To summarize, there is some evidence to suggest exogenous melatonin might be effective in elderly primary insomniacs who have low endogenous melatonin levels, but larger, well-controlled studies using rigorous sleep measures are needed.

Antidepressants

A number of antidepressants are widely used for the treatment of insomnia [41], often without evidence of a comorbid depressive disorder and despite the absence of convincing evidence demonstrating efficacy for the treatment of insomnia. The sedating antidepressants most commonly used to promote sleep are trazodone, amitriptyline, mirtazapine, and doxepin. None of these agents are active at the GABA receptor complex, but they do influence activity in other neurotransmitter systems that are or are suspected of being involved directly or indirectly in the control of sleep and wakefulness. Antihistaminergic and anticholinergic properties are thought to be particularly relevant to the sedating effects of antidepressants. Mirtazapine, trazodone, and the tricyclic antidepressants, particularly doxepin, are histamine receptor blockers. All of the tricyclic antidepressants have a relatively strong anticholinergic effect, particularly amitriptyline, imipramine, and doxepin. Serotonergic activity (eg, $5HT2_A$ antagonism) may also mediate some of the sedative effect of these drugs.

Trazodone

Trazodone was the most commonly identified medication for the treatment of insomnia in several large audits beginning in the early 1990s and maintained this prominent position until at least 2001–2002 [41,42]. Arguably, trazodone was perceived by prescribing physicians in that time period to be the agent of choice for the management of insomnia. This widespread and to a lesser extent continuing use is, however, clearly not evidence based, because trazodone's efficacy as a hypnotic for primary insomnia has been the focus of two at best mildly encouraging studies. In the first and smaller study, trazodone (150 mg) was administered nightly for 3 weeks to nine "poor sleepers" after an initial 2-week placebo period during which baseline sleep measures were established for comparison. There were decreases in stage 1 sleep and nocturnal arousals and increased slow-wave sleep in the treatment group, corresponding with improvements in subjective sleep quality. There were, however, no improvements in sleep latency or TST [43]. In a larger study using a parallel-group design comparing trazodone (50 mg) and zolpidem (10 mg) with placebo, trazodone improved both subjective sleep latency and TST, albeit to a smaller degree than zolpidem and only in the first of the 2 weeks of administration [44].

There are a larger number of studies investigating the hypnotic efficacy of trazodone in comorbid insomnia occurring in the setting of depression [42]. Most of these studies have multiple methodologic weaknesses, including lack of randomization or blinding, lack of adequate controls, or small numbers of participants. There are two randomized, double-blind, placebo-controlled studies in depressed outpatients. Trazodone (50 mg) or placebo was administered in a crossover design to seven depressed adults taking the monoamine oxidase inhibitor brofaromine (which caused or exacerbated a preexistent insomnia). There was a decrease in number of arousals and an increase in slow-wave sleep, but sleep latency and TST did not improve. All patients reported improved sleep quality, but only four of the seven wished to continue using trazodone after the study [45]. In a similarly designed crossover study with a placebo control, 17 depressed patients taking either fluoxetine or buproprion were treated with trazodone (50 or 100 mg) for a mean of 6.5 days. Although there was a significant improvement in global clinical ratings with active treatment, when individual items were considered, only sleep duration and early morning awakenings reached significance [46]. More encouraging results are reported in open-label studies, but the methodology prevents confident interpretation of findings.

In sum, studies of trazodone, over a large range of doses, generally are consistent in demonstrating patient reports of improvements in sleep quality, number of arousals, and, when PSG measures are used, amount of slow-wave sleep. Across studies, there is no consistent pattern of improvements in typical indicators of hypnotic efficacy such as time to sleep onset, amount of WASO, or TST, whether such parameters are assessed by PSG or patient report. Thus little evidence exists to support the use of trazodone as a treatment for insomnia, primary or otherwise.

Amitriptyline

Several small studies of amitriptyline for treatment of anxiety or depression with concurrent insomnia suggest some improvements in sleep quality [47–49]. These were open-label trials, however, and lacked both an adequate control group and PSG measures. Amitriptyline was compared with lorazepam in a randomized, double-blind fashion in 27 patients who had insomnia caused by opiate withdrawal. The patients were blind to drug but not to treatment, because there was no placebo control group. Sleep parameters were assessed by standardized questionnaire including the three sleep items of the Hamilton Depression Scale, indicating that patients responded equally well to either intervention [50]. The hypnotic efficacy and clinical effectiveness of amitriptyline for primary insomnia have not been investigated. The current data available regarding patients who have a psychiatric illness with concurrent insomniac complaints is not sufficient to support the use of amitriptyline in the management of sleep initiation or maintenance difficulty in this limited population or for insomnia in general. Amitriptyline was, however, the third most commonly used drug for the management of insomnia, based on the 2002 Verispan Physician Drug and Diagnosis Audit (Verispan, Yardley, PA) [41].

Doxepin

Doxepin has been more thoroughly investigated than other sedating antidepressants, based on three double-blinded, placebo-controlled studies of small to moderate size using PSG measures. In the first study, 47 primary insomniacs were randomly assigned to either doxepin (25–50 mg) or placebo nightly for 4 weeks in a parallel-group design. Sleep-quality ratings and PSG sleep efficiency were improved on the 2 PSG nights, night 1 and night 28. TST and WASO improved on night 1, but there was no significant difference in these measures between the treatment group and placebo by the end of the fourth week of treatment. Sleep latency in the treatment group at baseline was normal, however, and there were no significant improvements at later time points [51]. Intravenous doxepin (25 mg) administered to primary insomniacs on a single night in a double-blind crossover design increased TST and decreased sleep latency and WASO, relative to the placebo [52,53]. Significant, but smaller magnitude, improvements in these PSG measures seemed to persist when open-label doxepin (25 mg orally) was continued on a nightly basis for 3 weeks. Without a parallel control group, however, interpretation is difficult. One double-blind PSG study investigated the hypnotic efficacy of doxepin in insomniacs who had depression but did not include a parallel placebo group. Improvements in sleep latency, WASO, and TST occurred with doxepin (75–150 mg) administered nightly for 2 weeks, when comparison was made to baseline recordings done before the treatment period. The absence of a parallel control group limits the value of these findings [54]. In summary, there is suggestive evidence that doxepin improves sleep in insomniacs during acute administration, but appropriate dose–response studies of longer duration with adequate experimental control are needed.

Mirtazapine

Mirtazapine, an α_2-adrenergic, 5-$HT_{2A/C}$ and 5-HT_3 receptor antagonist, is a relatively new antidepressant with recognized sedating properties that are suspected to be mediated in part by antagonism of histamine type 1 receptors. The first published investigation specific to mirtazapine's sleep effect used a model of acute insomnia, in which mirtazapine (5, 10 or 15 mg), diazepam (10 mg) or placebo were administered in a double-blind fashion to individuals the night before expected surgery [55]. Ratings of sleep quality were improved with mirtazapine in a dose-dependent manner. PSG and quantitative measures were not used.

There have been several investigations of the effects of mirtazapine on the sleep of patients who have major depression without clinically diagnosed insomnia. None of the studies use rigorous methodology, which limits their value. A 2-week open-label study of nightly mirtazapine (15–30 mg) [56] without placebo control was further limited by a small sample size of six. Significant improvements in PSG sleep latency (even though the group at baseline had a latency of approximately 15 minutes) and TST were reported. Similar improvement in patient reports of sleep latency and TST were seen in a second trial of depressed patients randomly assigned to receive either a fixed 30-mg dose or an incrementing dose of 15 mg and then 30 mg, taken nightly for 2 weeks [57]. There was neither a placebo group

nor blinding to treatment. In an open-label study of depressed individuals, without a parallel placebo control, insomnia again was not an inclusion criteria, but a high proportion of the subjects indicated disturbed sleep consistent with insomnia on the Hamilton Depression Scale [58]. Sleep latency and TST were not reported, but WASO was reduced mildly with mirtazapine (30 mg) taken nightly for approximately 8 weeks. Finally, Winokur and colleagues [59] compared mirtazapine with fluoxetine over 8 weeks using a double-blind design and PSG measures but without a parallel placebo condition. There were significant improvements in PSG measures of sleep initiation and maintenance (sleep latency, WASO, TST, sleep efficiency) with mirtazepine after 2 weeks with the dose being titrated from 15 to 45 mg during the study. No PSG improvements were described for the fluoxetine group. In summary, the absence of any double-blind, placebo-controlled studies in insomnia patients with a range of doses prevents a determination of a role for mirtazepine in the treatment of insomnia.

In summary, there is a virtual absence of evidence from methodologically rigorous research that supports the efficacy of any antidepressant, at any dose, for the treatment of insomnia. Given the widespread use of antidepressants for insomnia, and their known safety risks, properly designed and controlled investigations are needed to provide evidence on which therapeutic decisions can be based.

Other prescription medications

Two of the newer antipsychotic medications, quetiapine and olanzapine, are used for the treatment of insomnia, presumably in patients who have major psychiatric disorders. No published investigations of either drug for the treatment of insomnia were identified, and meager information regarding the effects of olanzapine on sleep is available. In studies of healthy individuals and of patients who have schizophrenia, olanzapine seems to reduce wake time, increase slow-wave sleep, and improve ratings of sleep quality [60,61]. Clearly much additional research is needed before endorsing either drug for insomnia, especially given the potential for neurologic side effects.

The GABA-reuptake inhibitor tiagabine has been systematically investigated recently for the treatment of primary insomnia in a series of studies [62–64]. The PSG measures LPS and TST were not improved with tiagabine relative to placebo, and WASO was reduced in one of three studies. Slow-wave sleep was consistently increased in a dose-dependent manner across studies. Patient reports of sleep latency, TST, and WASO generally were not improved with tiagabine. Thus, tiagabine cannot be endorsed for the treatment of insomnia.

Nonprescription medications

There are no systematic data regarding the efficacy of antihistamines, alcohol, muscle relaxants, and valerian that support a role for these agents in the management of insomnia [65].

Summary

Efficacy in the treatment of insomnia has been demonstrated for the BzRA hypnotics. Ramelteon has been shown to be efficacious for insomnia characterized by difficulty with sleep onset. Because of the absence of abuse liability, ramelteon may be a viable alternative for individuals for whom concern for substance misuse is high, although it has not been tested in this population. Inadequate scientific evidence is available to conclude that melatonin, sedating antidepressants, antipsychotics, antihistamines, or other drugs are efficacious or should be recommended to treat insomnia. BzRAs have documented efficacy for acute or chronic insomnia in elderly as well as adult populations. In limited studies their effects in patients who have insomnia with comorbid conditions seem to be similar to those reported in research with primary insomnia. Among the BzRAs, the physician can use the differences in pharmacokinetic characteristics (and formulation) that determine duration of action to tailor treatment to the individual patient. There is accumulating evidence that BzRAs can be used effectively and safely for periods of up to 6 to 12 months, consistent with the experience of many physicians and patients and with the therapeutic requirements of a chronic disorder.

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