

Role of 5-HT_{2A} receptor antagonists in the treatment of insomnia

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Abstract: Insomnia encompasses a difficulty in falling asleep (sleep-onset insomnia) and/or a difficulty in staying asleep (SMI). Several selective serotonin-2A (5-HT_{2A}) receptor antagonists have been in development as potential treatments for SMI. However, none have shown a sufficiently robust benefit-to-risk ratio, and none have reached market approval. We review the role of the 5-HT_{2A} mechanism in sleep, the preclinical and clinical data supporting a role for 5-HT_{2A} receptor antagonism in improving sleep maintenance, and the status of 5-HT_{2A} receptor antagonists in clinical development. Overall, the polysomnography data strongly support an increase in slow-wave sleep and a decrease in waking after sleep onset following treatment with 5-HT_{2A} receptor antagonists, although it has been more difficult to show subjective improvements in sleep with these agents. The incidence and prevalence of SMI, whether primary or secondary to psychiatric, neurologic, or other medical conditions, will increase as our population ages. There will be an increased need for safe and efficacious treatments of insomnia characterized by difficulty maintaining sleep, and there remains much promise for 5-HT_{2A} receptor antagonism to play a role in these future treatments.

Keywords: 5-HT_{2A}, insomnia, serotonin, slow-wave sleep, wake after sleep onset

Introduction

Insomnia is defined as a complaint of poor quality sleep that is often associated with daytime fatigue, irritability, cognitive dysfunction, and general malaise.¹ Insomnia encompasses both a difficulty in falling asleep (sleep-onset insomnia) and/or a difficulty staying asleep (sleep-maintenance insomnia, SMI), both of which lead to nonrefreshing sleep. The DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision)² defines primary insomnia as a complaint of difficulty initiating sleep or maintaining sleep or of nonrestorative sleep of at least one month's duration and which causes significant distress or functional impairment, and is not secondary to another condition. The prevalence of primary insomnia is 1%–10% in the adult population, and up to 25% in the elderly.² In contrast, insomnia may be a feature of many other conditions and disease states (secondary insomnia). For example, insomnia related to other mental disorders is quite common, and can be reported as comorbid with major depressive disorder, dysthymic disorder, bipolar mood disorder, generalized anxiety disorder, schizophrenia, and others. Sleep disorders can also be secondary to general medical conditions, including neurologic disorders, cerebrovascular disease, endocrine dysfunction, viral or bacterial infections, pulmonary disease and coughing, and pain disorders. Insomnia, whether primary or secondary, and other sleep complaints increase with age and may affect up to 50% of the elderly.^{3,4}

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As the population of older adults increases, so does the need for effective insomnia treatments.

Cognitive behavioral therapy and pharmacotherapy, either alone or combined, are effective treatments to reduce insomnia.⁵ Cognitive behavioral therapy may be more effective overall than pharmacotherapy for the treatment of insomnia,⁶ although pharmacotherapy has a more immediate onset of effect.⁷ For persistent insomnia, the addition of medication to cognitive behavioral therapy can improve the acute response, although cognitive behavioral therapy appears to be better than pharmacotherapy at sustaining improvements in sleep over time.^{5,8} Current pharmacotherapy for the treatment of primary insomnia, characterized by difficulty falling asleep, includes benzodiazepines (such as triazolam and temazepam), nonbenzodiazepine modulators of gamma aminobutyric acid-A (GABA-A) receptors (such as zolpidem, eszopiclone, and zaleplon), or melatonin receptor agonists (ramelteon). Sedating antidepressants also are often prescribed off-label and used to improve symptoms of insomnia.^{9,10} Two drugs, extended-release zolpidem and eszopiclone, are currently approved in the US for the treatment of both sleep-onset insomnia and SMI.

Development of a drug that selectively targets sleep maintenance by decreasing the duration of wake after sleep onset (WASO) is greatly needed. The ideal sleep maintenance drug would also increase total sleep time without psychomotor impairment, abuse potential, and cognitive impairment. Many people have no trouble falling asleep, but wake in the middle of the night unable to fall back asleep or suffer from early morning wakefulness. For example, the overall prevalence of insomnia characterized by difficulty maintaining sleep is about 23%, whereas the prevalence of insomnia characterized by difficulty initiating sleep is only about 11%.¹¹ Patients with SMI only require a selective treatment that increases deep sleep, decreases the number of awakenings during the night, decreases the time spent awake during the night, and improves the quality of sleep so that they awaken feeling refreshed and cognitively alert. Drugs like eszopiclone may help people stay asleep during the night, but may require higher doses than those that help people with sleep-onset insomnia to fall asleep.¹² Moreover, while extended-release zolpidem may improve sleep early in the night, it can cause rebound early morning wakefulness (as indicated in its prescribing information package insert) and may not be appropriate for all patients. Non-GABAergic mechanisms have therefore been explored to provide a therapeutic alternative for selectively improving sleep maintenance. Low-dose doxepin, an antidepressant drug

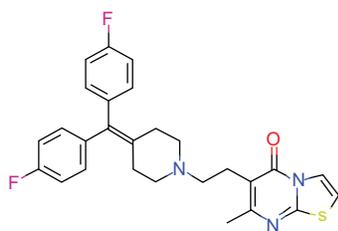
acting primarily as a histamine H₁ antagonist at low doses, has shown efficacy in the treatment of insomnia,¹³ and is the first drug approved by the Food and Drug Administration (FDA) for the selective treatment of SMI. However, better treatments for SMI are needed, with more robust efficacy and fewer side effects.

The present review focuses on the development of serotonin (5-HT) receptor 2A subtype (5-HT_{2A}) antagonists for the selective treatment of SMI. A number of drugs with this mechanism have been evaluated for effects on sleep in clinical trials. A list of these drugs is provided in Table 1 and their chemical structures are shown in the Figure 1. Many 5-HT_{2A} receptor antagonists are not silent or neutral antagonists, but rather exhibit intrinsic activity as inverse agonists (ie, activity in the opposite direction to receptor agonists).^{14,15} This inverse agonist activity essentially attenuates the basal constitutive signaling activity of 5-HT_{2A} receptors, in contrast with neutral antagonists that exhibit no negative intrinsic efficacy, but just occupy the receptor and block agonist-induced responses. However, because all inverse agonists can also block agonist-induced responses (ie, act as antagonists) and not all 5-HT_{2A} receptor antagonists have been evaluated in functional assays to determine intrinsic activity, both inverse agonists and antagonists will be referred to as antagonists in the present paper. Moreover, not all 5-HT_{2A} receptor antagonists discussed are selective for 5-HT_{2A} receptors. Selectivity for key compounds and implications for interpreting results will be discussed. However, selectivity data themselves have to be

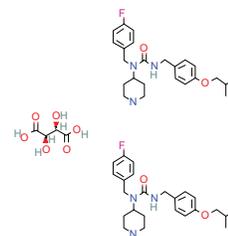
Table 1 Relative binding affinities for selective 5-HT_{2A} receptor antagonists. Potency values are expressed as pK_i, K_i (nM) or IC₅₀ (nM) as noted

	5-HT _{2A}	5-HT _{2C}	Development status
Ritanserin	pK _i 10.08 ^a pK _i 8.88 ^b	pK _i 9.36 ^a pK _i 7.61 ^b	Discontinued
Eplivanserin	pK _i 10.34 ^a pK _i 9.40 ^b	pK _i 8.87 ^a pK _i 6.13 ^b	Discontinued
Volinanserin	pK _i 10.52 ^a pK _i 9.76 ^b IC ₅₀ 0.3 ^c IC ₅₀ 0.39 ^d	pK _i 8.42 ^a pK _i 6.35 ^b IC ₅₀ 36 ^d	Discontinued
Pimavanserin	pK _i 9.3 ^a pK _i 9.7 ^b	pK _i 8.80 ^a pK _i 8.00 ^b	Phase III clinical development for indications other than insomnia
Nelotanserin	K _i 2.3 ^c K _i 0.4 ^d	K _i 221 ^c K _i 106 ^d	Discontinued
Pruvanserin	IC ₅₀ 1.0 ^c IC ₅₀ 0.35 ^d	IC ₅₀ 1334 ^d	Discontinued

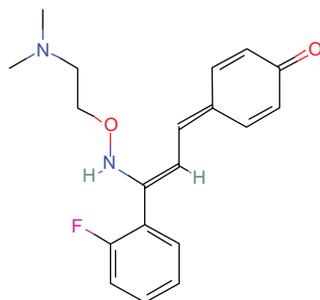
Notes: ^aMembrane binding pK_i,¹⁴ ^bwhole cell binding pK_i,¹⁴ ^ccloned rat receptor;^{33,39,77} ^dcloned human receptor.^{39,77}



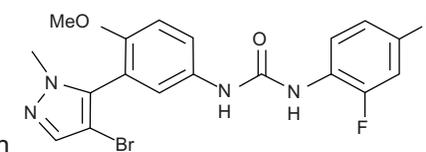
Ritanserin



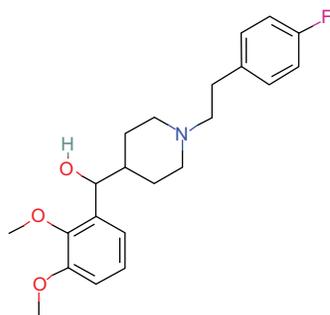
Pimavanserin (bitartrate)



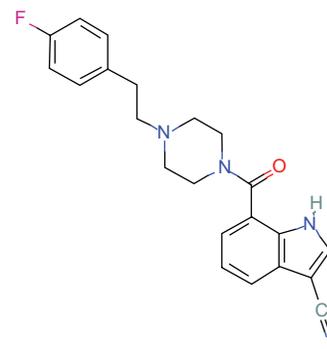
Eplivanserin



Nelotanserin



Volinanserin



Pruvanserin

Figure 1 Chemical structures of 5-HT_{2A} receptor antagonists.

interpreted with some caution because the affinity for a given receptor can vary with assay conditions. This has been shown to be the case for a variety of compounds tested for 5-HT_{2A} receptor affinity, with different potency and selectivity values for functional cell-based assays, membrane binding assays, and whole cell binding assays.¹⁴ Selectivity data were also reported differently, based on binding in receptor-enriched tissues, before receptor subtypes were cloned, and are dependent on relatively more or less selective radioligands. Subsequently, assays in cloned rat or cloned human receptor subtypes provided additional information regarding subtype selectivity.

Measurement of sleep parameters

Sleep architecture can be objectively quantified using polysomnography (PSG), electroencephalography (EEG), electro-oculography, and electromyography. These measures richly define the latency to and duration of each sleep stage and the number of cycles through the various stages of sleep that occur during the night. A scoring system for standardizing the measurement of sleep stages in humans has been developed, used extensively,¹⁶ and recently modified.¹⁷ Sleep consists of paradoxical sleep or rapid-eye movement (REM) sleep and nonrapid eye movement (non-REM) sleep. Non-REM sleep is divided into stages 1 and 2, and slow-wave

sleep (SWS). Sleep architecture changes with age, with some diseases/disorders, and with some drug treatment.

Although sleep stages can be measured using PSG in the laboratory, it is really the subjective complaints of difficulty in falling asleep, difficulty in maintaining sleep, and/or nonrefreshing or nonrestorative sleep that are associated with the significant distress or functional impairment that defines insomnia.² Thus, subjective measures are an important determinant of sleep quality but are difficult to measure systematically.

Localization and pharmacology of serotonin 5-HT_{2A} receptors

Serotonin has long been known to play a role in sleep.¹⁸ Serotonin receptors have been divided into many subclasses with different localization and function.¹⁹ The broad molecular biology and pharmacology of serotonin 5-HT_{2A} receptors have been critically reviewed elsewhere.²⁰ Of particular relevance to sleep, the 5-HT_{2A} receptor subtype has been suggested to play an essential role in maintaining the reciprocal inhibitory interactions between acetylcholine- and serotonin-containing neurons that mediate the sleep-wake cycle.²¹ The population of serotonergic neurons is diverse, with complex electrophysiologic differentiating features contributing to the sleep-wake cycle, including the existence of serotonergic neurons that exhibit slow clock-like activity that may be mediated in part by G protein-coupled cortical 5-HT_{2A} receptors.²² Tritiated eplivanserin-specific binding in the rodent brain was predominant in the prefrontal cortex, parietal cortex, occipital cortex, and striatum, with less specific binding in the hypothalamus, thalamus, hippocampus, and medulla oblongata, and no specific binding detected in the cerebellum.²³ Anatomic distribution of 5-HT_{2A} receptors, especially in neocortical areas in the primate brain, was confirmed using tritiated volinanserin and mRNA detected by *in situ* hybridization.²⁴ Using 5-HT₂ immunoreactivity, the distribution of 5-HT₂ receptors in the rat brain appears in high concentration in the basal forebrain, olfactory bulb, layer II of the piriform cortex, neostriatum, dorsal hippocampus, and the pedunculo-pontine and laterodorsal tegmental nuclei in the brainstem, with more sparse and even distribution in cerebral cortex.² Based on the distribution, localization, and morphology of the 5-HT₂-immunoreactive neurons, Morliak et al hypothesized that cortical GABAergic interneurons or cholinergic neurons express 5-HT₂ receptors.²⁵ Subsequent electrophysiologic data confirmed that serotonin increases GABA-evoked inhibitory activity, an effect blocked by 5-HT_{2A} receptor antagonism,^{26,27} and that 5-HT_{2A} receptors

mediate activity of interneurons in the piriform cortex in brain slices.²⁸ It is perhaps through the modulation of interneurons that 5-HT_{2A} receptors drive the balance between sleep and wakefulness. Consistent with this hypothesis, a 5-HT₂ receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), significantly increases wakefulness and reduces slow-wave sleep, effects that can be blocked by a 5-HT_{2A} receptor antagonist.²⁹

5-HT_{2A} receptor antagonists

Many 5-HT_{2A} receptor antagonists have been studied for their effects on sleep in animals and humans. Historically, one of the first compounds to be studied was ritanserin (6-[2-[4-[bis(4-fluorophenyl)methylene]-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one), first reported as a 5-HT₂ receptor antagonist with a mean IC₅₀ value of 0.9 nM.³⁰ Leysen et al reported that ritanserin had lesser, but measurable, affinity for histamine H₁ receptors (IC₅₀ 35 nM), dopamine D₂ receptors (IC₅₀ 70 nM), and adrenergic alpha₁ and alpha₂ receptors (IC₅₀ 97 nM and 150 nM, respectively). Later experiments revealed that ritanserin was relatively selective for 5-HT_{2A} over 5-HT_{2C} receptor subtypes¹⁴ (see Table 1). An extensive amount of preclinical and clinical data is available for ritanserin. These data provided an initial starting point for understanding the role of 5-HT_{2A} receptors in sleep, as described below. However, the clinical development of ritanserin was discontinued.

Eplivanserin (Ciltiyri[®], SR 46349B; trans, 4-[(3Z) 3-(2-dimethylamino-ethyl) oxyimino-3 (2-fluorophenyl) propen-1-yl] phenol hemifumarate), was previously in development by Sanofi-aventis which coined the term “ASTAR” (Antagonist of Serotonin Two A Receptors), in an effort to educate the public regarding this new mechanism of action for sleep aids. Also originally designated as a 5-HT₂ receptor antagonist,³¹ eplivanserin is even more selective than ritanserin for 5-HT_{2A} over 5-HT_{2C}¹⁴ (Table 1). Eplivanserin was reviewed by the FDA as a potential treatment for patients with chronic insomnia, but the FDA requested additional information regarding benefit-risk (sanofi-aventis press release, September 16, 2009) and development of the drug has been discontinued (sanofi-aventis press release, December 21, 2009).

Other selective 5-HT_{2A} receptor antagonists have been evaluated in clinical trials, such as volinanserin (M100907; (+/-) 2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol], pruvanserin (EMD 281014; 7-[4-[2-(4-fluorophenyl)ethyl]piperazine-1-carbonyl]-1H-indole-3-carbonitrile), nelotanserin (APD125; 1-[3-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methoxyphenyl]-3-(2,4-difluorophenyl)urea), and pimavanserin (ACP-103;

N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy[phenylmethyl]carbamide), but none have reached market approval. Volinanserin, another selective 5-HT_{2A} receptor antagonist in development by Sanofi-aventis, was discontinued in development (source: www.clinicaltrials.org). Pruvanserin development was also discontinued by Eli Lilly,³² although they are continuing development of a drug with a dual mechanism of action, ie, histamine H₁ antagonism and 5-HT_{2A} antagonism (HY10275). However, very little has been reported on the clinical effects of either compound. Along the same lines, esmirtazapine (ORG 50081; (S)-1,2,3,4,10,14b-hexahydro-2-methylpyrazino(2,1-a)pyrido(2,3-c)(2)benzazepine) combines 5-HT_{2A} receptor antagonism with H₁ receptor antagonism, and is in Phase III clinical development for insomnia, as well as for hot flashes associated with menopause. Again, little information regarding the clinical effects of esmirtazapine on sleep is available. Nelotanserin, a selective 5-HT_{2A} receptor inverse agonist, has also been discontinued (Arena Pharmaceuticals press release, December 9, 2008). Pimavanserin is in Phase III clinical development for the treatment of psychosis associated with Parkinson's disease, but is not being pursued for the treatment of sleep disorders after initial promising results in healthy volunteers (source: <http://www.acadia-pharm.com/>).

Additional selective 5-HT_{2A} receptor antagonists have been tested in animal models, but have not advanced to the clinic for the treatment of insomnia. Fananserin (RP 62203; 2-(3-(4-(p-Fluorophenyl)-1-piperazinyl)propyl)-2-H-naphth(1,8-cd)isothiazole 1,1-dioxide) is an example of a 5-HT_{2A} receptor antagonist with dopamine D₄ receptor antagonism which was evaluated in animal models for effects on sleep, but pursued in the clinic (and later discontinued) as an antipsychotic drug.³³ Other drugs with mixed pharmacology including 5-HT_{2A} receptor antagonism are also marketed, including atypical antipsychotic drugs and some antidepressant drugs. Some of these are prescribed off-label to improve sleep, but none have FDA approval for the treatment of insomnia.

5-HT_{2A} receptor antagonists and sleep in animal models

Ritanserin increases slow-wave activity and non-REM sleep in rats while decreasing REM sleep.³⁴⁻³⁷ Interestingly, ritanserin has the opposite effect, decreasing slow-wave sleep in cats.³⁸ The increase in slow-wave sleep caused by 5-HT₂ antagonists in rats appears to be more predictive of effects in humans than are the cat data (see below). Other 5-HT₂ receptor antagonists, such as Fananserin, pruvanserin, and

nelotanserin, have shown increases in non-REM or slow-wave sleep in rats,^{29,39,40} and eplivanserin and pruvanserin also show decreases in REM sleep in rats.^{29,31} The data with nelotanserin further suggest that 5-HT_{2A} receptor antagonism or inverse agonism is associated with increased sleep consolidation, as evidenced by a statistically significant increase in non-REM bout duration and a statistically significant decrease in the number of non-REM bouts in rats.³⁹ Nelotanserin also produced dose-dependent increases in delta power, a correlate of increased SWS. Importantly, repeated dose administration of nelotanserin did not result in the development of tolerance, and there was no evidence of rebound insomnia after cessation of dose administration of nelotanserin.³ Taken together, these data strongly support a role for 5-HT_{2A} in mediating sleep in animals.

A specific role for 5-HT_{2A} receptors in sleep was confirmed in 5-HT_{2A} receptor knock-out mice; increases in non-REM sleep induced by subtype-selective 5-HT_{2A} receptor antagonists, such as volinanserin, in wild-type mice were absent in 5-HT_{2A} receptor knock-out mice.⁴¹ Although others have suggested a role for 5-HT_{2C},⁴² independent confirmation of the increase of non-REM sleep in rats by the highly selective 5-HT_{2A} receptor antagonist, volinanserin, has been reported, providing supporting evidence for the role for 5-HT_{2A} in mediating non-REM sleep.⁴³ Moreover, increases in slow-wave sleep induced by the 5-HT_{2A/2C} receptor agonist, DOI, are blocked by a selective 5-HT_{2A} receptor antagonist, but not by a selective 5-HT_{2C} receptor antagonist.²⁹

Clinical efficacy of 5-HT_{2A} receptor antagonists

Ritanserin was the first selective 5-HT₂ receptor antagonist to be evaluated for effects on sleep in humans.^{44,45} An acute dose of ritanserin 10 mg increased slow-wave sleep (Stage 3 F[3,24] = 14.12, *P* < 0.01; Stage 4 F[3,24] = 10.67, *P* < 0.01) in healthy volunteers.⁴⁵ The increase in slow-wave sleep occurred at the expense of decreased Stage 2 sleep (F[3,24] = 18.25, *P* < 0.01) and decreased REM sleep (F[3,24] = 4.10, *P* < 0.05).⁴⁵ These data were in contrast with the benzodiazepine control, nitrazepam, which decreased deeper Stage 4 sleep and increased lighter Stage 2 sleep.⁴⁵ The effects of ritanserin on increasing slow-wave sleep appear to be dose-related, with the effects increasing across a dose range from 1 mg to 10 mg.^{46,47} Ritanserin increased slow-wave sleep by an average of 53 minutes, 82 minutes, 101 minutes, and 136.5 minutes at doses of 1, 3, 10, and 30 mg (F[5,54] = 26.75, *P* < 0.001).⁴⁸ There appears to be no tolerance to the sleep-enhancing effects of ritanserin

after repeated administration.^{44,48} The early studies lacked the statistical power to detect significant differences in subjective effects, although the effects measured by PSG were robust, even with such small sample sizes ($n = 4^4$ and $n = 9^4$). Interestingly, Idzikowski et al demonstrated that morning administration of ritanserin showed larger increases in SWS during the night (increase of about 94 minutes on average) than when ritanserin was administered just before bedtime (increase of about 52 minutes on average).⁴⁵ There was no psychomotor sedation during the day after morning administration of ritanserin, suggesting that ritanserin was acting via mechanisms that selectively mediate SWS with no effect on sleep initiation.

A single oral dose of eplivanserin 1 mg significantly increased slow-wave sleep by an average of about 61 minutes ($F[1,8] = 58.1, P < 0.01$) and decreased Stage 2 sleep by about 34 minutes ($F[1,8] = 6.4, P = 0.04$) in healthy volunteers ($n = 10$).⁴⁹ Although eplivanserin decreased the duration of WASO by an average of 9.5 minutes, the study was not sufficiently powered to be able to detect a statistically significant difference ($F[1,8] = 1.2, P = 0.31$). Eplivanserin did not significantly alter latency to sleep or latency to REM sleep, consistent with selective improvements in sleep maintenance. Although the efficacy of eplivanserin in a patient population has not been reported in a peer-reviewed journal, sanofi-aventis summarized the Phase III efficacy data used to support their New Drug Application (NDA) in a 2007 financial earnings summary report dated February 12, 2008. This report stated that eplivanserin significantly reduced patient-reported (subjective) WASO and patient-reported number of nocturnal awakenings in patients with primary insomnia. As mentioned above, the FDA reviewed the NDA of eplivanserin, but requested additional information regarding benefit-risk. Further details were not disclosed, but the development of eplivanserin was soon discontinued. Among 5-HT_{2A} receptor antagonists, eplivanserin was the most advanced compound in development. It is unclear what the confounding risks of eplivanserin are, but efficacy data from eplivanserin and other 5-HT_{2A} receptor antagonists appear to support the involvement of the 5-HT_{2A} receptor mechanism in maintaining sleep.

Nelotanserin, another selective 5-HT_{2A} receptor inverse agonist, at doses of 10 mg or 40 mg significantly decreased WASO by about 15 minutes on average ($P < 0.001$) after acute administration, but less robustly after one week of repeated administration ($P = 0.01$ for 10 mg and $P = 0.2$ for 40 mg).⁵⁰ The number of arousals decreased from an average of about 47 at baseline to about 39 after acute administration ($P < 0.0001$)

and remained significantly decreased at about 40 ($P < 0.0001$) after repeated administration of nelotanserin 40 mg in patients with primary insomnia.⁵⁰ Similarly, the number of awakenings decreased from about 10 at baseline to about seven or eight after acute ($P < 0.0001$) or repeated ($P < 0.0001$) administration of nelotanserin 40 mg, respectively.⁵⁰ These effects were associated with significant increases in slow-wave sleep (about 3% change from baseline and about 7% change from placebo at 10 mg, $P < 0.0001$, and about 4% change from baseline and about 8% change from placebo at 40 mg, $P < 0.0001$) in patients⁵⁰ and nearly doubling slow-wave sleep ($P < 0.01$) in healthy volunteers.³⁹ However, nelotanserin showed no dose-response relationship across a wide range of doses (10–40 mg)³⁹ and failed to show efficacy in a larger Phase IIB trial (Arena Pharmaceuticals press release, December 9, 2008). In the earlier trial, although nelotanserin significantly improved some subjective measures of sleep after acute administration, including decreased subjective number of awakenings ($P < 0.0002$), increased subjective total sleep time ($P = 0.01$), and improved sleep quality ($P = 0.01$), the magnitude of these changes was small (from an average of 3.0 subjective awakenings at baseline to an average of 2.3 after 40 mg nelotanserin; from an average of 4.96 hours of subjective total sleep time at baseline to 5.81 hours after 40 mg; from an average of 3.5 on the sleep quality index at baseline to an average of 2.7 after 40 mg), and did not maintain statistical significance after repeated administration.⁵⁰

Pimavanserin, a selective 5-HT_{2A} receptor inverse agonist in late-stage clinical development for the treatment of psychosis associated with Parkinson's disease, increased slow-wave sleep (nearly doubled after acute or two-week repeated administration, $P < 0.001$) in older adult healthy volunteers,^{51,52} but has not been evaluated in patients with insomnia. Consistent with the nonpsychomotor sedating mechanism, neither pimavanserin nor nelotanserin exhibited next-day cognitive deficits.^{39,50–52}

Hypnion reported that HY10275, a dual-acting H₁ receptor antagonist and 5-HT_{2A} receptor antagonist, improves WASO in patients with transient insomnia (Hypnion press release, January 5, 2007) before the company was acquired by Eli Lilly in April 2007. Since then, Lilly has discontinued clinical development of pruvanserin, its selective 5-HT_{2A} receptor antagonist,⁶ and continues development of HY10275, but no clinical data have been published in peer-reviewed journals on either compound. Volinanserin was originally in clinical development for the treatment of schizophrenia, and subsequently as a treatment for insomnia. Although clinical trials in patients with insomnia for volinanserin have been posted

on www.clinicaltrials.org, no clinical data on volinanserin's effects on sleep in humans have been published.

In the published literature taken together, the PSG data strongly suggest that 5-HT_{2A} receptor antagonism increases slow-wave sleep without psychomotor sedation and without effect on the initiation of sleep. The question arises as to the impact of increasing slow-wave sleep on the quality of sleep. It has been suggested that increasing deep, slow-wave sleep results in fewer awakenings during the night and reduced duration of wakefulness during the night (ie, when people do wake up, they fall back asleep quickly). However, increased slow-wave sleep does not necessarily correlate with subjective reports of deeper sleep or sleep quality, at least for drugs with other mechanisms, such as tiagabine.⁵³ In fact, the recommended practices for the evaluation of chronic insomnia include primarily subjective reports and detailed sleep histories, rather than PSG evaluation.¹ Therefore, drug development efforts need to target improvements in subjective sleep. There are limited data for 5-HT_{2A} receptor antagonists in studies sufficiently statistically powered in order to be able to measure subjective improvements in sleep. However, data suggest that 5-HT_{2A} receptor antagonism can improve subjective sleep.⁵⁴ Moreover, 5-HT_{2A} receptor antagonists may improve clinical symptoms of depression, anxiety, and/or psychosis in specific patient populations.^{55,56} These data suggest a potentially unique clinical opportunity for this neurochemical mechanism, as discussed in more detail below.

Ritanserin increases slow-wave sleep (nearly doubled from an average of 69 minutes at baseline to an average of 129 after ritanserin, $F[3,24] = 17.9$, $P < 0.0001$) and improves subjective quality of sleep ($F[4,32] = 4.48$, $P = 0.006$) in middle-aged poor sleepers.⁵⁷ Similar findings (an average of 133 minutes of slow-wave sleep after ritanserin compared with placebo at an average of 77 minutes, $P < 0.05$) were documented in young poor sleepers.⁵⁸ Ritanserin also has demonstrated benefit in patients with narcolepsy.⁵⁴ Although ritanserin did not affect the number of sleep attacks compared with placebo in an adjunctive study in patients with narcolepsy, treatment with ritanserin for four weeks did significantly increase slow-wave sleep (average decrease of 0.8 minutes from baseline for placebo compared with an average increase of 9.3 minutes after ritanserin 5 mg [$P = 0.001$] compared with an average increase of 10 minutes after ritanserin 10 mg [$P = 0.001$]) and increased self-reports of feeling refreshed (average rating for placebo of 1.3 compared with 0.9 after ritanserin 5 mg [$P = 0.019$] or compared with 1.0 after ritanserin 10 mg [$P = 0.021$]).⁵⁴

Even though ritanserin did not increase total sleep time in healthy volunteers (only increased SWS with a commensurate decrease in Stage 2 sleep), ritanserin could significantly increase total sleep time in patients exhibiting a deficit in sleep. For example, in abstinent alcoholics with dysthymia and exhibiting less than six hours sleep/night at baseline, ritanserin treatment for 2–4 weeks significantly increased total sleep time (placebo at second week showed no change in total sleep time, compared with an average 47 minute increase from baseline with ritanserin [$P < 0.05$]; placebo at the fourth week showed an average five-minute increase from baseline in total sleep time, compared with an average 48-minute increase with ritanserin [$P < 0.05$]).⁵⁵ WASO was also reduced ($P < 0.05$) after only four weeks of treatment with ritanserin, and sleep efficiency improved ($P < 0.05$) after two or four weeks in these patients.⁵⁵ Importantly, symptoms of depression and anxiety were also significantly reduced by ritanserin; Hamilton Depression Scale scores were reduced by greater than 50% ($P = 0.01$) and Hamilton Anxiety Scale scores were similarly reduced ($P = 0.01$).⁵⁵

Some psychiatric disorders are associated with disrupted sleep patterns. Ritanserin increases slow-wave sleep in patients with generalized anxiety disorder⁵⁹ and in patients with depression,⁶⁰ with a similar magnitude of effect as that seen in healthy volunteers. However, one study demonstrated that the increase was predominantly in Stage 3 sleep with no significant effect on Stage 4 sleep in depressed patients, whereas healthy volunteers show an increase in both Stage 3 and Stage 4 sleep, and combined Stage 3 + Stage 4, defined as SWS.⁶¹

Despite some differences in response to 5-HT₂ antagonism between healthy subjects and patient populations, 5-HT₂ receptor antagonists have been shown to normalize sleep disturbances characterized by fragmented sleep and frequent awakenings. For example, in dysthymic patients with fragmented superficial sleep, higher Stage 2 sleep and lower slow-wave sleep, ritanserin (10 mg once daily in the morning for four weeks) significantly increased the proportion of time spent in slow-wave sleep compared with placebo in a double-blind study.⁶² Ritanserin also increased the number of transitions from lighter sleep stages to deeper, slow-wave sleep. Although a relationship between clinical improvement in dysthymic symptoms as a consequence of increased slow-wave sleep has not been determined, depressed patients may benefit from normalized sleep.

Looking at the clinical data for the 5-HT_{2A} receptor antagonists, there is considerable evidence to support a role for 5-HT_{2A} receptor antagonism in the treatment of insomnia

characterized by difficulty maintaining sleep. In general, 5-HT_{2A} receptor antagonists increase deep slow-wave sleep, decrease WASO, and decrease the frequency of arousals and awakenings during the night (Table 2). Together, these data suggest improved sleep maintenance and improved sleep efficiency, and potential benefit in special psychiatric populations. 5-HT_{2A} receptor antagonists are generally well tolerated. A summary of common side effects is provided in Table 2, and a more detailed discussion of safety and tolerability is described below.

Safety and tolerability

As mentioned above, 5-HT₂ antagonism does not cause psychomotor sedation or motor incoordination. Unlike benzodiazepines that impair psychomotor function and memory retention, ritanserin has little effect on measures of psychomotor and cognitive function.⁶³ Withdrawal symptoms from benzodiazepines and GABA-A mediated drugs can be a safety issue and can require slow tapering from the drug when discontinuing. Treatment with 5-HT₂ receptor antagonists does not appear to be associated with adverse effects upon withdrawal.⁶⁴ Moreover, there is no evidence of tolerance to 5-HT₂ receptor antagonists^{44,48} and, therefore, no need for progressively increased doses to maintain efficacy over time with repeated administration.

The only adverse events reported with four weeks of ritanserin 5 mg/day in patients with narcolepsy were headache and pre-existing sleep/wake problems.⁵⁴ In abstinent alcoholics with dysthymia, side effects with ritanserin 10 mg/day reported included numbness to touch, impaired coordination, constipation, dry mouth, dizziness, and increased appetite, but each side effect was only reported in one subject.⁵⁵ In a study investigating the effects of ritanserin for the treatment of schizophrenia in an open-label setting, the most frequent adverse events that were not present at baseline included palpitations, drowsiness, micturition disturbances, headache, and pruritus.⁶⁵ In a large (n = 423) Phase III clinical trial evaluating the efficacy of ritanserin in the treatment of alcohol dependency, the most frequent adverse events were

fatigue, headache, rhinitis, constipation, and insomnia.⁶⁶ A dose-related statistically significant prolongation of the QTc interval was observed in this study. It is likely that this safety issue contributed to the discontinuation of development of ritanserin, although it is also likely that this was a compound-specific safety issue and not a “class effect”, because it has not been reported as a safety concern for other 5-HT₂ receptor antagonists.

The dose-limiting side effect of pimavanserin in healthy volunteers was nausea and vomiting.⁶⁷ Another common side effect of pimavanserin was postural dizziness.⁶⁷ Dizziness, nausea, and vomiting were also side effects observed with nelotanserin in patients with insomnia.⁵⁰ Fatigue and headache were also more common with nelotanserin treatment than with placebo.⁵¹

Fananserin was first identified as a 5-HT₂ receptor antagonist⁶⁸ and later identified as having potent 5-HT_{2A} and dopamine D₄ receptor affinity.³³ It was evaluated clinically as an antipsychotic,⁶⁹ but failed to show efficacy for the treatment of schizophrenia and, therefore, was never pursued for the treatment of sleep disorders. In patients with schizophrenia, the dose-limiting side effect of fananserin was hypotension.⁷⁰

The most extensive and relevant safety data were probably collected during the extensive development programs for eplivanserin and volinanserin that reached Phase III clinical development for the treatment of insomnia. Those data, however, are not publically available.

Patient perspectives

An insomnia treatment that focuses on maintaining normal restorative sleep during the night and feeling rested and alert upon awakening and throughout the day remains an important unmet medical need. Many patients with insomnia have no trouble falling asleep, but awaken during the night unable to fall back asleep. A great many of these patients do not want or need a sedating drug that can be associated with a multitude of side effects, such as motor slowing (that can contribute to falls), cognitive dulling, and next-day hangover effect. The risk associated with abuse and dependence is an additional cause for concern. A large number of patients with SMI likely remain untreated due to the desire to avoid the side effects associated with sleep-inducing drugs.

On the other hand, it may be the lack of a sedating discriminative stimulus that has hampered the ability of 5-HT_{2A} receptor antagonists to achieve the kinds of profound subjective improvements in sleep, as their effects on EEG sleep patterns would suggest. In other words, patients who

Table 2 Positive effects on sleep and side effects common to 5-HT_{2A} receptor antagonists

5-HT _{2A} receptor antagonism	
Positive effects on sleep	Side effects
Increased deep slow wave sleep	Dizziness/hypotension
Decreased wake after sleep onset	Fatigue
Decreased number of arousals/awakenings	Headache
Improved sleep maintenance	Nausea/vomiting
Improved sleep efficiency	Constipation

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are used to taking a sleep aid that makes them feel drowsy or sedated may not think that they are receiving a beneficial effect on sleep when given a 5-HT₂ antagonist that lacks these effects. This could confound subjective reports of sleep habits. If this is the case, dual-acting drugs for sleep initiation and sleep maintenance may fare better in larger clinical trials than selective sleep-maintenance drugs. Still, these kinds of drugs do not selectively target the need for improved sleep maintenance without additional pharmacology and the accompanying additional safety risks associated with off-target drug interactions. Alternatively, it may be simply that the right 5-HT_{2A} receptor antagonist with sufficient efficacy at safe doses has yet to be developed. It remains an enigma that 5-HT_{2A} receptor antagonists have such profound effects on sleep, yet so many drugs have failed in larger efficacy trials or have failed to show a sufficiently robust benefit to risk ratio in clinical trials.

Future treatment options

The selective treatment of SMI remains a goal yet to be achieved by 5-HT_{2A} receptor antagonists. The currently available 5-HT_{2A} receptor antagonists fail to show robust efficacy in large clinical trials. This may arise from an inherent limit of the impact of blocking this receptor on sleep mechanisms, problems with the drugs such as poor pharmacokinetics, dose-limiting side effects, insensitive clinical measurement approaches, or a combination of these factors. Better and different drugs are clearly needed. One approach that has been taken is to develop compounds opportunistically that possess 5-HT_{2A} receptor antagonism combined with other receptor interactions. The focus to date has been on developing compounds that combine sleep-onset with sleep-maintenance properties, such as the H₁ antagonist/5-HT_{2A} antagonist approach. However, this approach may be misguided. As noted above, many patients with insomnia do not need nor want the troubling side effects of a hypnotic agent. A better approach might be to search for drugs with receptor interactions that act synergistically to maintain sleep but do not possess hypnotic effects. We have recently studied a unique compound, ITI-007, for its ability to improve sleep selectively in patients with SMI. At low doses, ITI-007 acts primarily as a serotonin 5-HT_{2A} receptor antagonist. At higher doses, ITI-007 also acts as a dopamine D₂ receptor partial agonist presynaptically, as an antagonist postsynaptically, and as a serotonin transporter inhibitor. In our study, ITI-007 decreased WASO and increased SWS in patients with insomnia in a dose-dependent manner.⁷¹ ITI-007 promotes natural, restorative

sleep over the course of the night, with significant increases in SWS early in the night and significant increases in Stage 2 sleep late in the night and towards morning, with no early morning wakefulness and no impairment of next-day functioning. These data suggest that this compound may have improved efficacy for treating sleep maintenance insomnia and that the additional pharmacology beyond 5-HT_{2A} receptor antagonism may be beneficial. The magnitude of these effects increased with dose, with dramatic improvements seen at the highest tested dose (10 mg). At this dose, 5-HT_{2A} receptors are fully saturated and interactions with dopamine receptors and the serotonin transporter begin to emerge. It is possible, therefore, that ITI-007 robustly maintains sleep above and beyond that provided by 5-HT_{2A} receptor antagonism through these additional target interactions. At these doses, ITI-007 does not induce sleep or impair next-day cognitive performance. These findings give hope that, as we better understand the neurobiologic underpinnings of sleep maintenance problems, we may be able to develop more targeted drugs with combination mechanisms that will maintain natural sleep patterns without inducing unwanted off-target side effects.

Conclusions

The incidence and prevalence of SMI will increase as our population ages. There will be an increased need for safe, efficacious, and selective treatments of insomnia characterized by difficulty maintaining sleep. Moreover, many psychiatric, neurologic, and other medical conditions are associated with SMI that remains largely untreated. Although there is much promise for selective 5-HT_{2A} receptor antagonists to provide selective therapy for SMI, none have yet achieved the robust efficacy required for marketing approval. The corporate reasons for discontinuation of development of any given drug are not always transparent. However, it appears that many 5-HT_{2A} receptor antagonists have lacked a sufficient benefit to risk ratio, whether it be due to lack of efficacy or safety concerns. Safety concerns, as discussed above, do not appear to be necessarily target-mediated. This would suggest that 5-HT_{2A} receptor antagonism remains a viable mechanism for the treatment of SMI. In addition to an improved safety profile, challenges in development that need to be overcome include clinical trial designs able to measure more effectively the subjective sleep maintenance and improvement of quality of life that may be associated with improved sleep maintenance. Now that low-dose doxepin has been approved by the FDA for the selective treatment of SMI, the regulatory pathway has been established. Whether a selective 5-HT_{2A}

receptor antagonist can meet or beat the bar that has been set is yet to be seen.

By better understanding the neurobiologic basis of SMI, better drugs may be discovered. Still, a lot can be learned from dissecting the actions of nonselective drugs that also possess activity as 5-HT_{2A} receptor antagonists. Atypical antipsychotics are a rich source for this latter endeavor. Data from clinical trials support the improvement of sleep by these drugs in special populations. For example, ziprasidone increases slow-wave sleep and improves sleep continuity in healthy volunteers,⁷² olanzapine increases slow-wave sleep and improves sleep continuity in healthy volunteers and in patients with depression,^{73,74} and risperidone⁷⁵ and paliperidone⁷⁶ improve sleep in patients with schizophrenia. While these drugs are unlikely to be used to treat SMI in the wider sense, understanding their impact on fundamental sleep mechanism may be revealing and may provide a direction for future drug development approaches. Yet, there remains a need for the development of better drugs for the treatment of insomnia characterized by difficulty maintaining sleep. Antagonists of the 5-HT_{2A} receptors may play an important role in the development of improved treatment of these kinds of sleep disorders.

Acknowledgments

The authors would like to thank Drs S Mates and P Greengard for their helpful comments.

Disclosure

KEV is a paid employee of Intra-Cellular Therapies, Inc. and is a former paid employee of ACADIA Pharmaceuticals Inc. RED is a paid consultant to Intra-Cellular Therapies, Inc., a former paid consultant and former paid employee of ACADIA Pharmaceuticals Inc. Intra-Cellular Therapies, Inc., and ACADIA Pharmaceuticals are developing investigational new drugs.

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