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Drugs for Insomnia beyond Benzodiazepines: Pharmacology, Clinical Applications, and Discovery

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ABBREVIATIONS: AUC, area under the curve; BZDs, benzodiazepines; CHMP, Committee for Medicinal Products for Human Use; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; EEG, electroencephalogram; 5-HT, serotonin; KO, knockout; LC, locus coeruleus; LDT/PPT, lateralpontine tegmentum/pedunculopontine tegmental nuclei; MDD, major depressive disorder; MNPO, median preoptic nucleus; NREM, non-rapid eye movement sleep; OX, orexin; PRM, prolonged-release melatonin; PSQI, Pittsburgh Sleep Quality Index; PTSD, posttraumatic stress disorder; RCT, randomized-controlled trial; REM, rapid eye movement sleep; RT, reticular thalamus; SCN, suprachiasmatic nuclei; SDL, sublaterodorsal nuclei; SSRI, selective serotonin reuptake inhibitor; SWS, slow-wave sleep; vlPO, ventrolateral preoptic area; WASO, wake after sleep onset; WT, wild type.

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***Abstract*——Although the GABAergic benzodiazepines (BZDs) and Z-drugs (zolpidem, zopiclone, and zaleplon) are FDA-approved for insomnia disorders with a strong evidence base, they have many side effects, including cognitive impairment, tolerance, rebound insomnia upon discontinuation, car accidents/falls, abuse, and dependence liability. Consequently, the clinical use of off-label drugs and novel drugs that do not target the GABAergic system is increasing. The purpose of this review is to analyze the neurobiological and clinical evidence of pharmacological treatments of insomnia, excluding the BZDs and Z-drugs. We analyzed the melatonergic agonist drugs, agomelatine, prolonged-release melatonin, ramelteon, and tasimelteon; the dual orexin receptor antagonist suvorexant; the modulators of the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels, gabapentin and pregabalin; the H_1 antagonist, low-dose doxepin; and the histamine and serotonin receptor antagonists, amitriptyline, mirtazapine, trazodone, olanzapine, and quetiapine. The pharmacology and mechanism of action of these treatments and the evidence-base for the use of these drugs in clinical practice is outlined along with novel pipelines. There is evidence to recommend suvorexant and low-dose doxepin for sleep maintenance insomnia; there is also sufficient evidence to recommend ramelteon for sleep onset insomnia. Although there is limited evidence for the use of the quetiapine, trazodone, mirtazapine, amitriptyline, pregabalin, gabapentin, agomelatine, and olanzapine as treatments for**

insomnia disorder, these drugs may improve sleep while successfully treating comorbid disorders, with a different side effect profile than the BZDs and Z-drugs. The unique mechanism of action of each drug allows for a more personalized and targeted medical management of insomnia.

I. Introduction

A. Insomnia as a Public Health Burden

Insomnia is a significant public health burden, increasing work absenteeism and health care costs in a large proportion of the population. It causes altered cognition, emotional disturbances, and reduced quality of life (Zammit et al., 1999; Wickwire et al., 2016). Insomniacs commonly complain of irritability, daytime sleepiness, low energy and motivation, physical discomfort, and impaired cognitive functioning (Buysse et al., 2007; Fortier-Brochu et al., 2012; Morin and Jarrin, 2013), not to mention deficits in working memory, episodic memory, and some aspects of executive functioning (Fortier-Brochu et al., 2012).

The prevalence rate of insomnia in the general population has been estimated as low as 5% to as high as 50% (Ohayon, 2002; Morin and Jarrin, 2013). Most epidemiologic studies have found that about one-third of adults (30%–36%) report at least one symptom of insomnia, like difficulty initiating sleep or maintaining sleep; this rate drops to 10%–15% when daytime consequences, like excessive daytime sleepiness, are added to the definition (Ohayon, 2002; Morin and Jarrin, 2013). From 1999 to 2010, the number of prescriptions for any sleep medication increased by 293% (Ford et al., 2014). Strong increases in the percentage of office visits resulting in a prescription for second generation benzodiazepines or Z-drugs (zopiclone, zolpidem, or zaleplon) sleep medications (~350%), benzodiazepine receptor agonists (~430%), and any sleep medication (~200%) were noted (Ford et al., 2014).

B. Changes in the Nosology of Insomnia in Diagnostic and Statistical Manual of Mental Disorders-V

The publication of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association, 2013) fundamentally changed the landscape of sleep medicine and the diagnosis of insomnia. In DSM-IV, primary insomnia was distinguished from insomnia that is secondary to another diagnosis, including major depressive disorder and generalized anxiety disorder. DSM-IV understood secondary insomnia as a symptom of a primary psychiatric disease: the secondary insomnia was expected to normalize with treatment of the primary disorder (American Psychiatric Association, 2013). However, clinical research has established that this "secondary" insomnia is often resistant to treatment of the primary disorder: in the STAR*D trial, after remission with a course of citalopram therapy, 54.9% of remitters continued to experience midnocturnal insomnia and 71.7% continued to experience sleep disturbance in some form (Nierenberg et al., 2010). DSM-5 has eliminated primary insomnia as a diagnosis in favor of insomnia disorder, which may occur alongside other diagnoses like major depressive disorder. This revised definition obliges the clinician to treat insomnia as a comorbidity, rather than a symptom of a primary illness. In this review, we use the term "insomnia disorder," except when a published study explicitly states that it analyzes patients with "primary insomnia."

C. Clinical Guidelines for Insomnia Treatment and the Necessity of a Translational Approach

New evidence-based clinical practice guidelines for the treatment of insomnia disorder were recently published in *The Journal of Clinical Sleep Medicine* (Sateia et al., 2017a), representing the first comprehensive, systematic analysis of single agents for the treatment of insomnia disorder, developed using the GRADE methodology (Grading of Recommendations, Assessment, Development, and Evaluation) (Sateia et al., 2017b). Unfortunately, the level of evidence for all of the authors' recommendations was "weak." This evaluation means that the strength of the evidence in the published data were low. Notably, all of the recommended treatments for sleep onset insomnia besides ramelteon are Z-drugs or BZD hypnotics. For sleep maintenance insomnia, three of five of the treatment options are Z-drugs or BZDs.

The dearth of strong published evidence led us to adopt a translational approach in exploring treatments for insomnia disorder, integrating the neurobiological mechanism of action of each drug gleaned from basic science and integrating it with reported clinical data and current medical practice. This approach is currently the standard in pharmacological research and is a priority for federal and foundational grants. Although clinical research is critical for establishing evidence-based guidelines for treatment, knowledge gleaned from basic research can be helpful for the clinical judgment of the therapeutic efficacy of hypnotics and the treatment of psychiatric comorbidities (Comai et al., 2012a,b).

In this review, we will focus on drugs that are not BZDs or Z-drug, because an extensive literature already exists. Our approach will be translation, offering alternatives to BZDs and Z-drugs. We will also describe novel hypnotic compounds and pharmaceutical pipelines.

D. The Dark Side of Benzodiazepines and Z-Drugs and the Off-Label Use of Other Drugs

Although the market for insomnia medications continues to be dominated by BZDs and Z-drugs, both categories of drug have numerous problematic effects as short-term treatment and, in particular, as long-term therapy. BZDs are associated with hangover effects the next day, cognitive or memory impairment, the rapid development of tolerance, rebound insomnia upon discontinuation, car accidents or falls, and a substantial risk of abuse and dependence (Foy et al., 1995; Hemmelgarn et al., 1997; Soldatos et al., 1999; Ashton, 2005). A large proportion of people prescribed BZD drugs become chronic users. Furthermore, BZDs are a factor in approximately 5%–10% of car accidents, although the rate in individual studies varies from 1% to 65% (Thomas, 1998).

Z-drugs also cause cognitive impairments: case control studies find that BZD or Z-drug use approximately doubles the risk of being involved in a motor vehicle accident (Thomas, 1998; Gunja, 2013b). They can produce dependence (Lugoboni et al., 2014) as well as next-day cognitive, memory, psychomotor and balance impairments (Mets et al., 2011).

The problems with BZDs have led clinicians to prescribe other medications that are perceived to be less harmful or to be less liable to addiction. As an example, in the United States in 2002, the antidepressant medication trazodone was the most commonly prescribed medication for insomnia, with 34% more prescriptions than the most commonly prescribed FDA-approved treatment (Walsh, 2004). The Prescriber National Summary Report, Calendar Year 2014 pools data from all the Medicare recipients in the United States. In one cross-sectional study of American adults, 3% of 32,328 people used a "prescription medication commonly used for insomnia" in the previous month: 38% of those who received a hypnotic medication received Z-drugs, 31% trazodone, 17% BZDs, 11% quetiapine, and only 5% received doxepin (Bertisch et al., 2014). This study confirms that drugs prescribed off-label are very common in the treatment of insomnia, despite the low number of randomized, controlled trials (RCTs).

II. Sleep Architecture

In mammals, physiological sleep is divided into two strikingly distinct states known as non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Historically, NREM sleep was subdivided into four stages (stages 1, 2, 3, 4) defined according to different electroencephalogram (EEG) patterns (Rechtschaffen and Kales, 1968). According to the manual of the American Academy of Sleep Medicine published in 2007 (Iber et al., 2007), NREM sleep is now divided into three progressively deeper stages of sleep named stage N1, stage N2, and stage N3 (formerly stages 3 and 4). REM sleep is now officially referred to as stage R. The EEG pattern in NREM sleep is synchronous and presents characteristic waveforms: sleep spindles, K-complexes, and high-voltage slow waves. Stage N1 accounts for 2%–5% of total sleep time and is the phase of transition between the awake state and sleep. Stage N2 accounts for 45%–55% of total sleep time and occurs throughout the entire sleep period. The descent from stage N1 to stage N2 is characterized by a decrease in the frequency of the EEG trace paralleled by an increase in its amplitude. The EEG hallmark of N2 are theta waves. N2 is also characterized by the occasional occurrence of a series of high-frequency waves (8–14 Hz) known as sleep spindles, generated by interactions between thalamic and cortical neurons (De Gennaro and Ferrara, 2003), and fast and high-amplitude wave forms known as K-complexes also occur (Amzica and Steriade, 2002). According to Rechtschaffen and Kales' (1968) criteria, a K-complex is defined as a negative slow wave immediately followed by a positive wave exceeding 0.5 seconds in duration.

As stage N2 sleep progresses, high-voltage, slow-wave activity appears as the subject enters stage N3. Stage N3, which corresponds to deep or delta-wave sleep and reflects slow-wave sleep (SWS), occurs mostly in the first third of the night and accounts for 5%–15% of total sleep time. During this sleep stage, there is a further fall in blood pressure, a slowing of breathing, and a reduction in body temperature, with reduced muscle activity, although muscles maintain their tonus and thus some movements can be observed.

Stage R or REM sleep is defined by low-amplitude desynchronized theta EEG activity and represents 20%–25% of total sleep time. It occurs in four to five episodes throughout the night and is characterized by complete disappearance of muscle tone paradoxically associated with a cortical but also hippocampal activation and rapid eye movements. Since REM sleep EEG activity closely or paradoxically resembled the EEG of alert-waking subjects, this sleep stage has been also referred as paradoxical sleep, particularly in studies conducted in animals.

In physiological conditions, the activity of the brain over the course of the night proceeds from waking through the three stages of NREM sleep and then REM sleep. NREM sleep and REM sleep continue to alternate through the night in a cyclical fashion, usually with a total of four to five sleep cycles throughout the night. Importantly, as sleep progresses, the time spent in stage N3 becomes shorter, whereas the time spent in REM gets longer. The average length of the first NREM-REM sleep cycle is between 70 and 100 minutes and that of the second and later cycles is about 90–120 minutes. Sleep architecture, including the duration of the different stages as well as the duration of a NREM-REM cycle, is strongly dependent on the

subject's age. With aging, humans tend to experience an increase in the latency to fall asleep, more fragmented sleep, and less time spent in SWS, particularly in the early cycles of sleep. One of the parameters providing information concerning sleep fragmentation is the "sleep efficiency index" that is a measure of the percentage of total time in bed actually spent sleeping and is calculated by the sum of the time spent in sleep stage N1, N2, N3, and REM, divided by the total time spent in bed. Specific details on the changes in the sleep structure occurring during aging are outside the scope of this paper but are analyzed in a comprehensive recent review written by Mander et al. (2017). Restorative sleep is not only dependent on an adequate duration of sleep; the physiological architecture of sleep must be conserved. Under certain conditions and with certain pharmacological treatments, the total duration of sleep may remain unchanged or increased, but deviations from normal sleep architecture generate increased sleep fragmentation. Disturbances in subjects' sleep architecture results in a sense of having had nonrestorative sleep and is associated with next-day impairments in conducting daily activities. Unfortunately, most of the drugs currently used as hypnotics—in particular benzodiazepines, but also Z-compounds to a lesser extent—disturb sleep architecture (Bastien et al., 2003; Gunja, 2013a).

III. The Receptor-Mediated Mechanism of Action of Hypnotics

Drugs currently used to treat insomnia mainly act on specific ionotropic or G-protein-coupled receptors located in specific brain areas. Each receptor modulates different characteristics of sleep. It is thus important for the clinician to understand the mechanism of action of each hypnotic to target better its effect in individual patients. This translational approach helps to build a more personalized medicine, targeted to the patient, that overcomes the limitations of overarching clinical guidelines. While guidelines tend to homogenize the patient population, a translational approach based on the mechanism of action of each drug may help to target the individual patient and his or her particular comorbidities.

A. GABA Receptor

The most studied receptors in the treatment of insomnia are the $GABA_A$ receptors, GABA being the chief inhibitory neurotransmitter in the mammalian nervous system, where BZDs and Z-drugs act. BZDs and Z-drugs act as positive allosteric modulators at the $GABA_A$ binding site, potentiating GABA's inhibitory effect (Stahl, 2008). The combination of GABA at the receptor's agonist site and benzodiazepine-receptor agonists at the allosteric site increases the frequency of the chloride channel opening to an extent that does not occur with GABA alone (Stahl, 2008). The result is neuronal inhibition. Similar to other ligand-gated ion channels, the $GABA_A$ receptor is composed of five subunits belonging to different subunit classes (α1–6, β1–3, γ1–3, δ, ε, θ, π) that are distributed throughout the brain differentially; there is also some interindividual variability in their localization. For a detailed review on this topic, please see Olsen and Sieghart (2009). In this way, BZDs and Z-drugs exert their effects as sedatives, anxiolytics, anticonvulsants, muscle relaxants, and hypnotics. The main difference between BZDs and Z-drugs is in their receptorial affinities toward the different $GABA_A$ subunits. BDZs show similar affinity to the α1, α2, α3, and α5 receptor subtypes. In contrast, most of the Z-drugs show higher affinity for a subset of the alpha subunits, mainly the α1 receptor subtype, that seems to be specifically implicated in sleep but not in anxiety. Zaleplon, zopiclone, and zolpidem have high affinity and potency for the α1 subunit and low affinity and potency at α_2 and α_3 subunits; eszopiclone—the (*S*)-enantiomer of zopiclone —has high affinity and potency for the α2 and α3 subunits (Nutt and Stahl, 2010). Due to their selective agonism, Z-drugs mainly produce sedative and hypnotic properties and likely display improved tolerability over the BZDs (Wilson and Nutt, 2007).

This review will focus on alternate mechanisms of action that are not directly mediated through GABA receptors, with the exception of the gabapentinoids (pregabalin and gabapentin). Although pregabalin and gabapentin are analogs of GABA, they do not bind directly to $GABA_A$ or benzodiazepine receptors. Instead, they inhibit the $\alpha_2\delta$-1 subunit voltage-dependent calcium channels. They have been found to increase SWS sleep in patients diagnosed with epilepsy and insomnia (Bazil et al., 2012) and healthy adults (Foldvary-Schaefer et al., 2002; Hindmarch et al., 2005). Further development of novel $\alpha_2\delta$ calcium channels like atagabalin (PD 200390) was pursued for the treatment of insomnia but then discontinued following unsatisfactory trial results (Springer Adis Insight, 2017).

B. Serotonin Receptors

The 5-HT-containing neurons of the dorsal raphe nuclei discharge maximally during waking and decrease their firing during SWS; they cease firing during REM sleep, similar to the norepinephrine-containing neurons of the locus coeruleus (Jones, 2005). The $5\text{-}HT_{1A}$ agonist OH-DPAT, which decreases 5-HT firing activity by activating its autoreceptors (Gobbi et al., 2001) increases REM sleep (Portas et al., 1996). Although $5\text{-}HT_{1A}$ receptors are autoreceptors located at the somatodendritic level, $5\text{-}HT_{1B}$ receptors are autoreceptors localized at postsynaptic sites. $5\text{-}HT_{1B}$ receptors are also used as heteroceptors in many cells throughout the brain to inhibit the release of neurotransmitters other than serotonin (Marek, 2010). Furthermore,

serotonergic neurons attenuate cortical activation through inhibitory influences on other neurons of the activating systems, including acetylcholine-containing neurons (Jones, 2005).

C. Serotonin 2 Receptors

The 5-HT_2 receptor is located in the prefrontal and orbitofrontal cortex, the (subgenual) anterior cingulate cortex, the occipital, and parietal cortex (van Dyck et al., 2000; Adams et al., 2004; Hinz et al., 2007); in the nucleus accumbens, olfactory tubercule, and the hippocampus (Pompeiano et al., 1994; Barnes and Sharp, 1999; López-Giménez et al., 2001); and in the locus coeruleus, areas that are important for both sleep modulation and mood regulation (Szabo and Blier, 2001).

At the cellular level, 5-HT_{2A} receptors are located on apical dendrites on pyramidal cells and, particularly in subcortical regions, on local (GABAergic) interneurons (Jakab and Goldman-Rakic, 1998; Barnes and Sharp, 1999; Aghajanian and Sanders-Bush, 2002). Although the mechanism of action of 5-$HT_{2A/2C}$ receptor antagonists has yet to be fully elucidated, it is likely that they promote SWS via a reduction of inhibitory input to the cells of the ventrolateral preoptic nucleus that fire during sleep. Through postsynaptic 5-HT_{2A} receptors on GABAergic cells of the reticular thalamus, serotonergic fibers from the dorsal raphe and supralemniscal nucleus (B9) modulate the reticular thalamus that in turn regulates sleep and wakefulness (Rodrìguez et al., 2011).

Recent studies with more subtype-selective 5-HT_{2A} and 5-HT_{2C} receptor ligands (antagonists and inverse agonists), as well as experiments in knockout (KO) mice, support a role for 5-HT_{2A} receptor subtypes in promoting SWS and the 5-HT_{2C} receptor in promoting REM (Popa et al., 2005).

Ritanserin, a potent antagonist of the serotonin receptors 5-HT_{2A} and 5-HT_{2C}, has been found to increase SWS in healthy volunteers to a greater degree than ketanserin (a drug with less potent effects as an antagonist of the 5-HT_{2C} receptor, used clinically as an antihypertensive) (Sharpley et al., 1994). Ritanserin was never commercialized for safety problems, although it did show efficacy at increasing SWS and delta activity in young male poor sleepers (Viola et al., 2002), underlining the importance of these receptors in the regulation of SWS.

Interestingly, many hypnotic drugs prescribed off-label (trazodone, mirtazapine, olanzapine, quetiapine) act through 5-HT_{2A} and 5-HT_{2C} receptors to enhance sleep (Landolt and Wehrle, 2009). Trazodone, the first 5-HT_{2A} antagonist, was initially developed as an antidepressant, but is currently one of the most common hypnotics prescribed in the clinic (Bertisch et al., 2014). Similarly, the 5- and 10-mg doses of olanzapine compared with placebo, significantly increased SWS, sleep continuity measures, and subjective sleep quality (Sharpley et al., 2000). See Tables 1 and 2 for the receptorial affinities of each drug and for their effects on sleep architecture, respectively.

D. Serotonin 1A Receptors

The 5-HT_{1A} receptor is the main 5-HT autoreceptor, located at the somatodendritic level of the 5-HT neurons of the dorsal raphe as well as at synaptic terminals in the hippocampus and prefrontal cortex. 5-HT_1 knockout (KO) mice have increased 5-HT firing activity (Richer et al., 2002) and decreased REM sleep, but not SWS (Boutrel et al., 2002); the 5-HT_{1A} agonist OH-DPAT induces a decrease in REM sleep in the first 2 hours after injection followed by an increase in REM after 6–8 hours (Boutrel et al., 2002). 8-OH-DPAT (1.0–4.0 μg) injected into the dorsal raphe nucleus increased slow-wave sleep and decreased wakefulness, although its administration of subcutaneously induced biphasic effects such that low doses decreased wakefulness and increased slow-wave sleep while higher doses induced opposite effects, perhaps due to the opposing effects of the 5-HT_{1A} autoreceptors and heteroreceptors (Monti and Jantos, 1992). Given these opposing and complex effects, employing 5-HT_{1A} partial agonists is a rational approach to insomnia, given their capacity to act as agonists when the levels of endogenous agonist are low and as antagonists when the levels of endogenous agonist are high.

5-HT_{1B} knockout mice have increased REM sleep and lower SWS during the light phase and lack REM sleep rebound after deprivation, suggesting that the blockage of 5-HT_{1B} receptors increases REM and decreases NREM sleep (Boutrel et al., 1999). In agreement with this finding, in wild-type (WT) mice, the 5-HT_{1B} agonists CP 94253 and RU 24969 induced a dose-dependent reduction of paradoxical sleep during the 2–6 hours after injection, whereas the 5-$HT_{1B/1D}$ antagonist GR 127935 enhanced paradoxical sleep (Boutrel et al., 1999).

Quetiapine and trazodone both act on 5-HT_{1A} receptors as partial agonists (Richelson and Souder, 2000; Odagaki et al., 2005).

E. Noradrenaline Receptors

Similarly to 5-HT neurons, the norepinephrine-containing neurons of the locus coeruleus (LC) nuclei discharge maximally during waking and decrease their firing during SWS; they are nearly silent during paradoxical or REM sleep (Jones, 2005).

The most important adrenergic receptors implicated in sleep are α_1 and α_2 receptors. α_2 Receptors are located at presynaptic terminals, acting as the main norepinephrine neuron autoreceptors, although they are also present at the postsynaptic terminal. The activation of the α_2 autoreceptor decreases LC activity, while, in contrast, α_2 receptor blockade using α_2 antagonists increases the

TABLE 1
Summary of main molecular targets of hypnotic drugs
Mechanism-of-action details can be found in the text of this review, in review articles (Sanger, 2004; Wilson and Argyropoulos, 2005; Sills, 2006; Stahl, 2009), and/or in the summary of product characteristics for each individual drug.

Drug	5-HT$_1$	5-HT$_2$	5-HT$_3$	5-HT$_7$	α_1	α_2	MT$_1$/MT$_2$	OX$_1$/OX$_2$	H$_1$	5-HTT	NET	D$_1$	D$_2$	D$_4$	m$_1$	Voltage-Gated Ca^{2+} Channels	GABA$_A$
Ramelteon							X										
Tasimelteon							X										
Melatonin prolonged-release							X										
Agomelatine		X					X										
Low-dose doxepin					X				X						X		
Suvorexant								X									
Trazodone	X	X			X				X	X							
Amitryptiline					X				X	X	X				X		
Quetiapine	X*	X*		X*					X*		X*	X*	X		X*		
Olanzapine		X			X				X			X	X	X	X		
Gabapentin																X	
Pregabalin																X	
Mirtazapine		X	X		X	X			X								
Benzodiazepines																	X
Z-compounds																	X

*Binding mainly due to its metabolite norquetiapine.

firing activity of LC neurons (Gobbi and Blier, 2005). In fact, although the α_2 agonist clonidine decreases LC activity and thus promotes sleep (particularly SWS) while inhibiting REM (De Sarro et al., 1987; Berridge et al., 2012), there is evidence that the selective α_2 antagonist yohimbine increases wakefulness, at least in rats (Mäkelä and Hilakivi, 1986).

However, selective knockdown of α2A-adrenergic receptors in the LC abolished α_2 agonist dexmedetomidine-induced loss-of-righting-reflex, but not sedation (Zhang et al., 2015). These findings implicate other structures besides the LC in α_2 receptorial regulation of arousal: these structures include the preoptic area, in which α_2 receptors are situated on GABAergic interneurons, which influence sleep through reciprocal inhibitory projections to the W systems; or the prefrontal cortex, where α_2 receptors are likewise situated on GABAergic neurons (Manns et al., 2003; Luppi et al., 2017).

Indeed, when GABAergic neurons ("OFF neurons") containing α_2 receptors located in the prefrontal cortex are stimulated during SWS, their firing activity ceases, which likely produces paradoxical or REM sleep (Manns et al., 2003). This complex α_2 receptor-mediated mechanism may account for the manner in which the α_2 antagonist mirtazapine promotes sleep, although it increases LC firing (Gobbi and Blier, 2005).

The α_1 and beta adrenergic receptors are also involved in the regulation of arousal. While individual administration of the α_1 blocker prazosin produces decreased behavioral arousal and individual administration of the beta noradrenergic antagonist timolol has no effect, coadministration of prazosin and timolol produces a substantial, synergistic increase in slow-wave firing activity with a corresponding strong sedative effect behaviorally (Berridge and Espana, 2000).

F. Dopamine Receptors

Dopamine neurons are also active during wakefulness and decrease during REM sleep and SWS (Monti and Monti, 2007). In particular, the dopamine D_2 receptor is one of the main receptors involved in sleep regulation. D_2KO mice exhibit a significant decrease in wakefulness, with a concomitant increase in NREM and REM sleep and a drastic decrease in low-frequency electroencephalogram delta power (0.75–2 Hz) of NREM sleep, especially during the first 4 hours following lights off. In agreement with these findings, the D_2 antagonist raclopride mimicked these effects in WT mice (Qu et al., 2010). Similarly, the dopamine D_2 receptor antagonists haloperidol and chlorpromazine have the tendency to induce sleepiness in human subjects, while blockers of the dopamine transporter like amphetamine and modafinil increase wakefulness by increasing extracellular levels of dopamine in the synapse (Schmitt and Reith, 2010). In contrast, paradoxically, the antiparkinsonian D_2 agonist ropinirole

TABLE 2
Summary of the effects of the different hypnotic drugs on the sleep architecture and their potential to induce dependence liability

Drug	Latency to Sleep Onset	Effect on NREM Sleep			Effect on REM Sleep	Sleep Efficiency	Dependence Liability
		Stage N1	Stage N2	Stage N3 also referred as SWS			
Benzodiazepines	↓	↓	↑	↓	↓	↑	High
Z-drugs	↓	↔	↑	↔	↔	↑	Moderate
Ramelteon	↓	↔	↑	↓	↔	↑	Low
Tasimelteon	↓	n.a.	n.a.	n.a.	↑	↑	Low
Melatonin prolonged-release	↓	↔	↔	↔	↔	↑	Low
Agomelatine	↓	↔	↔	↑	↔	↑	Low
Low-dose doxepin	↓	↔	↑	↔	↔	↑	Low
Suvorexant	↓	↔	↑	↔	↑	↑	Low
Trazodone	↔	↔/↓	↔/↓	↔/↑	↔/↓	↔	Low
Amitryptiline	↓	n.a.	n.a	↑	↓	↑	Low
Quetiapine	↓	↔	↑	↔↓	↓	↑	Low
Olanzapine	↓	↔	↔/↑	↑	↓/↔/↑	↑	Low
Gabapentin	↔	↔	↔	↑	↔	↑/↔	Moderate
Pregabalin	↓	↔	↔	↑	↓	↑	Moderate
Mirtazapine	↔	↓	↔	↑	↔	↑	Low

↑: Increase; ↓: decrease; ↔: no change. n.a.: not assessed.

also induces sleepiness, but mostly daytime sleepiness and sleep attacks during the day (Paus et al., 2003), likely through activation of D_2 autoreceptors that decrease DA firing activity during the daytime.

G. Orexin Receptors

The orexins (OXs), also known as the hypocretins, are a pair of excitatory neuropeptide hormones with approximately 50% sequence homology: orexin-A and orexin-B (hypocretin-1 and -2). They are produced exclusively by a population of neurons in the lateral hypothalamic area (de Lecea et al., 1998; Sakurai et al., 1998). Physiological effects of the OXs in the brain result from the activation of two G-protein-coupled receptors, named orexin 1 (OX_1) and orexin 2 (OX_2) receptors (Sakurai et al., 1998). OX_1 has one-order higher affinity for OX-A than for OX-B, whereas OX_2 binds OX-A and OX-B with similar affinities.

The orexinergic system is known to promote behavioral arousal, increase food intake and locomotor activity (Sakurai et al., 1998; Nakamura et al., 2000), and induce wakefulness (Hagan et al., 1999). In addition, the OXs appear to regulate the stress response by increasing the activity of the hypothalamic-pituitary axis (Al-Barazanji et al., 2001). Furthermore, they are implicated in the pathophysiology and treatment of depressive-like behavior (Nollet et al., 2011).

KO animals that lack the prepro-orexin gene, OX_2 gene, or orexin neurons have narcolepsy-like behavior, including fragmentation of sleep/wakefulness, direct transitions from wake to REM sleep, and sudden loss of muscle tone while still awake (cataplexy) (Chemelli et al., 1999; Lin et al., 1999; Hara et al., 2001; Willie et al., 2003). However, OX_1 KO mice have mild or almost no abnormality in the regulation of sleep and wakefulness, suggesting that the orexin signal through OX_2 has a more critical role in the regulation of sleep and wakefulness, especially in the maintenance of arousal. The expression pattern of orexin receptors matches the afferent projections of orexin neurons throughout the brain. The few studies using selective antagonists of the OX_1 and OX_2 receptors have demonstrated that selective blockade of OX_2, but not OX_1, increases REM and NREM. However, coadministration of the selective OX_1 antagonist and the selective OX_2 antagonist intensified the effect of OX_2 blockade on REM and NREM (Dugovic et al., 2009). Other studies have agreed that OX_1 may play a role in the regulation of sleep and arousal (Mieda et al., 2011).

A novel orexin antagonist (suvorexant) was recently put on the market and other selective orexin antagonists are under development (Winrow and Renger, 2014).

H. Melatonin Receptors

The neurohormone melatonin activates two G-protein-coupled receptors, MT_1 and MT_2. Melatonin is implicated in circadian rhythms and sleep regulation, but the differential role of its individual receptors remains undefined.

Melatonin receptors have a specific localization that implicates them in physiological functions related to sleep (Lacoste et al., 2015). MT_2 receptors are located in the reticular thalamus, an area involved in modulating SWS (Steriade et al., 1993), as well as the substantia nigra (pars reticulata), supraoptic nucleus, red nucleus, and the CA_2, CA_3, CA_4 areas of the hippocampus and SCN (Ekmekcioglu, 2006; Ochoa-Sanchez et al., 2011), while MT_1 is located in the locus coeruleus, the dorsal raphe, and areas CA2 and CA3 of the hippocampus and SCN (Lacoste et al., 2015).

Recently our group has better characterized the differential role of each receptor in sleep function using MT_1KO, MT_2KO, and double MT_1-MT_2KO as well as selective MT_2 ligands (Comai et al., 2013). MT_2KO mice have a selective disruption of SWS during the inactive

phase and increased wakefulness, whereas MT_1KO mice have a selective disruption of REM during the inactive phase and an increase of NREM. These results elucidate the opposing and differential effects of the two receptors in the neurobiology of sleep.

Dual MT_1-MT_2 KO mice only show a small increase in wakefulness, without a difference in total sleep compared with their WT counterparts (Comai et al., 2013), establishing that the MT_1 and MT_2 receptors may have opposing roles. This interpretation fits with the fact that melatonin and drugs that bind both MT_1 and MT_2 only modify the time to induction of sleep, without a global effect on total sleep time or sleep architecture (Comai et al., 2015). Thus, the absolute benefit of melatonin compared with placebo is smaller than other pharmacological treatments for insomnia (Ferracioli-Oda et al., 2013). Similarly, ramelteon, a dual agonist of both MT_1 and MT_2, has only been approved by the FDA for the treatment of insomnia characterized by difficulty with sleep onset; it does not affect total sleep duration or increase SWS.

I. Histamine Receptors

The sole source of brain histamine is neurons localized in the hypothalamic tuberomammillary nuclei (Haas and Panula, 2003). These neurons project axons to the whole brain, although functionally distinct histaminergic neural circuits differentially influence individual brain regions. Four histamine receptors have been identified: H_1, H_2, H_3, and H_4 (Takahashi et al., 2002). In general, histamine modulates inflammatory responses through peripheral H_1 receptors and modulates gastric acid secretion through peripheral H_2 receptors. This led to the discovery and therapeutic use of potent selective H_1 and H_2 receptor antagonists. In contrast to the H_1, H_2, and H_4 receptors, the H_3 receptor is predominantly expressed in the CNS (Lovenberg et al., 1999; Oda et al., 2000), acting as an autoreceptor on presynaptic neurons and controlling histamine turnover. H_3 receptors have also been shown to act as heteroreceptors in dopamine-, serotonin-, noradrenaline-, GABA-, and acetylcholine-containing neurons (Schlicker et al., 1994).

The H_1 receptor is probably the most important physiological histamine target in the maintenance of waking. In animal studies, H_1 receptor agonists increase wake duration (Passani and Blandina, 2011). H_1 receptor KO mice show fewer incidents of brief awakening (<16-second periods), prolonged durations of NREM sleep episodes, a decreased number of state transitions between NREM sleep and wakefulness, and a shorter latency for initiating NREM sleep. When the H_3 receptor antagonist ciproxifan was administered intraperitoneally to WT mice, wakefulness increased in the mice in a dose-dependent manner but did not increase at all in H_1KO mice, highlighting the interdependent functional relationship between H_1 and H_3 receptors (Huang et al., 2006).

H_3KO mice show clear signs of enhanced histaminergic neurotransmission and vigilance, with higher EEG θ power during spontaneous wakefulness and during behavioral tasks. During the dark period, they display deficient wakefulness and signs of sleep deterioration, such as pronounced sleep fragmentation and reduced cortical slow activity during SWS, which occurs due to a desensitization of postsynaptic histaminergic receptors as a result of constant histamine release (Gondard et al., 2013).

Prescription drugs like mirtazapine, quetiapine, and hydroxyzine—not to mention nonprescription sleep aids like diphenhydramine—act on histaminergic neurons.

J. Other Receptors

Other receptors involved in sleep, but which remain to be pharmacologically exploited, include the adenosine A_1 and A_2 receptors (Jacobson and Gao, 2006). Interestingly, the arousal effect of the adenosine antagonist caffeine is mediated through the adenosine A_{2A} receptor, but not the A_1 receptor (Huang et al., 2005).

Adenosine mediates the somnogenic effects of prior wakefulness and likewise plays an important role in the regulation of the duration and depth of sleep after wakefulness (reviewed by Greene et al. (2017). Pharmacological data suggest that A_{1A} receptors are involved in the regulation of sleep, although a lack of A_{1A} receptors is not sufficient to prevent homeostatic regulation of sleep (Stenberg et al., 2003). It is conceivable that although the A_{1A} receptor is an important factor for sleep regulation in normal animals, other factors, such as the A_{2A} receptor, may compensate for the absence of the A_{1A} receptor when it is deleted in knockout models. Indeed, it has been shown that the A_{2A} receptor has a key role in adenosine-mediated sleep-promoting effects (Urade et al., 2003).

Melanin-concentrating hormone (MCH) neurons are known to be active during REM sleep and the stimulation of these neurons promotes REM sleep; indeed, electrophysiological recordings of MCH neurons across the natural sleep-wake demonstrates that they do not fire during waking, fire occasionally during NREM sleep, and fire maximally during REM sleep (Hassani et al., 2009). Importantly, they are colocalized with orexin neurons in the lateral hypothalamic area and adjacent zona incerta but as unique cell populations spatially intermingled with each other (reviewed by Yamashita and Yamanaka (2017).

Importantly, when MCH neurons are active, they inhibit orexin neurons, and knockout of MCH peptide and the MCHR1 receptor in mice produces less REM and NREM sleep. Optogenetic studies have confirmed the role of MCH neurons in inducing REM sleep: optogenetic activation of these cells during NREM sleep produces REM, but activation during wakefulness produces no effect. MCH neurons also play a role in NREM sleep, because temporally controlled ablation of

these cells increases wakefulness and decreases NREM sleep duration without affecting REM sleep (Tsunematsu et al., 2014).

K. From Receptors to Sleep Circuits.

The manner in which unique neurotransmitters and individual brain areas reciprocally interact is still not understood in its entirety. The neural circuits that generate arousal and sleep (both NREM and REM) remain to be completely elucidated.

Humans are diurnal mammals, with a circadian clock that promotes wakefulness during the day, even as homeostatic sleep drive builds up. Importantly, sleep timing is phase-linked to intrinsic circadian rhythm-controlled temperature rhythms as well as extrinsic light and dark signaling (Scammell et al., 2017).

In mammals, the circadian rhythm is organized by the suprachiasmatic nuclei (SCN). The retinohypothalamic tract, which contains the intrinsically photosensitive retinal ganglion cells and the photopigment melanopsin, projects directly and monosynaptically to the SCN via the optic nerve and the optic chiasm. The SCN, which is rich in MT_1 and MT_2 receptors (Lacoste et al., 2015), projects to the paraventricular nucleus, and the "darkness" signal is eventually relayed to sympathetic fibers that innervate the pineal gland, which produces melatonin in response to darkness. Melatonin then stimulates the brain's MT_2 receptors in the NREM sleep activating regions of the brain: the reticular thalamus and the preoptic areas, including both the ventrolateral preoptic area (vlPO) and the median preoptic nucleus (MNPO) (Ochoa-Sanchez et al., 2011; Lacoste et al., 2015). Specifically, the MNPO appears to regulate the firing activity of the vlPO (Chou et al., 2002). It has been shown that during the transition from wakefulness to sleep, the MNPO—which specifically contains neurons that fire during slow-wave and paradoxical sleep, with slow discharging activity <5 Hz—begin to fire not before, but after, sleep onset, with a gradual increase in discharge rate (Sakai, 2011). During NREM sleep, the vlPO sends inputs that act to reduce the activity of the orexinergic arousal system and the monoamine nuclei (including the ventral tegmental area containing DA neurons, the dorsal raphe containing 5-HT neurons, and the LC containing NE neurons) by releasing the inhibitory neurotransmitters GABA and galanin. As a feedback mechanism, vlPO neurons receive reciprocal inputs from the arousal nuclei, including the ventral tegmental area, dorsal raphe, and LC; the vlPO also receives input from the histaminergic tuberomammillary nucleus (Adamantidis et al., 2010).

The reticular thalamus (RT) is another area essential for NREM sleep: people suffering from fatal familial insomnia show thalamic disruption that inactivates their ability to sleep, which is paralleled by a dysfunction in melatonin production (Portaluppi et al., 1994). RT neurons discharge in burst activity exclusively during NREM, and thalamocortical pathways project this synchronous burst activity, intermingled with periods of silence, onto the cortex. This rhythmic firing activity generates the synchronized EEG pattern typical of SWS, which produces disconnection between the cortex and the outside world (Steriade and Timofeev, 2003). The RT is also rich in melatonin MT_2 receptors, which are likely activated at the beginning of sleep (Ochoa-Sanchez et al., 2011). Disconnection between the prefrontal cortex and sensory input is greatest during Stage 4 of NREM sleep, when the frequency of the EEG trace is the lowest and its amplitude is the highest. Conversely, during wakefulness, the RT and thalamocortical neurons are depolarized by inputs from the reticular activating system of the brain stem and discharge instead with a tonic activity (adapted from Steriade et al., 1993; Purves et al., 2004).

REM sleep, in contrast, is regulated by other brain areas. Many researchers have hypothesized that REM sleep is mediated mostly through cholinergic neurons located in the lateralpontine tegmentum/peduncolopontine tegmental nuclei (LDT/PPT). These neurons are active during REM sleep and generate the cortical activation and atonia typical of this sleep stage and are inactive during NREM sleep. Indeed, LDT/PPT neurons send inputs to the ventromedial medulla, which inhibits motor neurons by releasing GABA and glycine into the spinal and brain stem motor neurons, producing atonia. LDT/PPT neurons are also the main source of acetylcholine to the thalamus: activation of this acetylcholine pathway depolarizes thalamic neurons, generating the cortical activation associated with REM sleep and dreaming. Other nuclei important for REM sleep regulation are 1) the sublaterodorsal nucleus (SDL), which produces GABA and glutamate and projects to the glycinergic/GABAergic premotor neurons in the ventromedial medulla and ventral horn of the spinal cord, and through these circuits likely inhibits motor neurons during REM sleep, and 2) the MCH-containing neurons that fire during REM sleep and decrease their activity during NREM sleep and wakefulness. The "REM-off versus REM-on" theory of REM sleep hypothesizes that during the REM-on period, LDT/PPT, SDL, and MCH neurons are active and inhibit monoamine neurons as well as motor neurons, while during the REM-off period, the vlPAG/LPT is inhibited by MCH neurons and other neurotransmitters (Saper et al., 2001; reviewed in España and Scammell, 2011).

Other cholinergic nuclei that are active during REM sleep and wakefulness include the basal forebrain and the lateral hypothalamus; these same nuclei are inhibited during NREM sleep.

The manner in which the brain alternates cycles of NREM and REM remains unknown, although some researchers have proposed the existence of a mutually inhibitory circuit between vlPAG/LPT and the SDL.

Figure 1 is a schematic representation of nuclei important during sleep, illustrating the circuits that modulate the sleep/wake cycle and their respective receptors.

IV. Melatonergic Drugs

A. Agomelatine

1. Mechanism of Action. Similar to melatonin, agomelatine inhibits firing activity in the SCN, likely through its full agonist activity at MT_1; it is also an agonist at the MT_2 receptor (McAllister-Williams et al., 2010). Agomelatine has low affinity for the 5-HT_{1A} and 5-HT_{2B} receptors, and its effects are thought to be mediated by its antagonism of the 5-HT_{2C} receptor, with a pK_i of 6.2 at human receptors (Millan et al., 2003). In animals, chronic administration of agomelatine produces a dose-dependent increase in dopamine and norepinephrine levels in the frontal cortex, without an effect on serotonin (European Medicines Agency, 2008a); like many other antidepressants, agomelatine administration is associated with increased expression of brain-derived neurotrophic factor mRNA and enhanced neurogenesis in the hippocampus (Banasr et al., 2006). In one study, agomelatine given at the onset of the late phase induced no changes in rat polygraphic recordings. However, when it was administered shortly before dark phase, agomelatine (10 and 40 mg/kg) enhanced the duration of REM and SWS sleep and decreased the duration of the wake state for 3 hours (Descamps et al., 2009). A summary of the pharmacological targets of agomelatine is reported in Table 1.

2. Pharmacokinetics. Agomelatine is rapidly and well-absorbed following oral administration (>80%) (European Medicines Agency, 2016). However, absolute bioavailability is low and variation between individuals is substantial, with increased bioavailability in women compared with men. Elderly people likewise experience greater exposure to the drug, with AUC and C_{max} 4- and

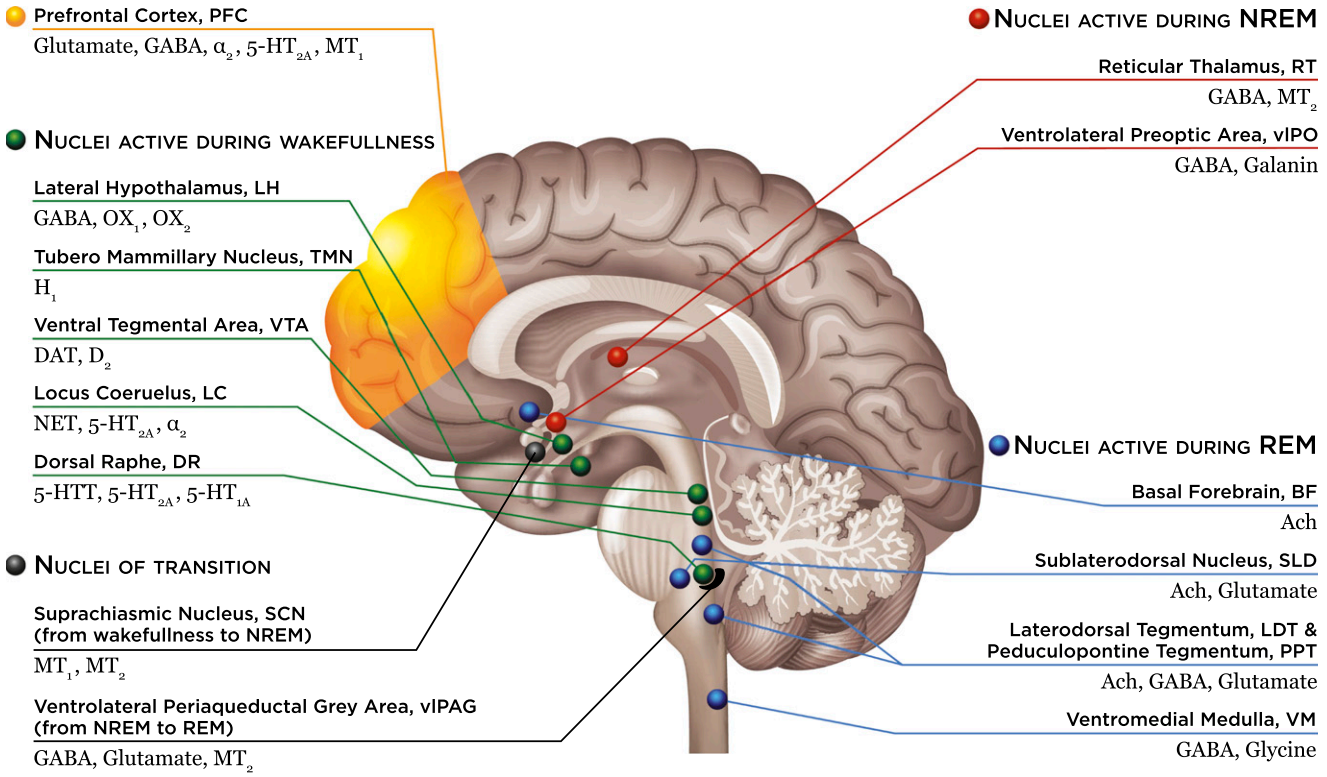

Fig. 1. Brain areas involved in the regulation of sleep and wakefulness with their respective receptors. Top left, green: When the brain enters NREM, neurons of the arousal system decrease their firing activity. This includes the serotonin neurons of the dorsal raphe (DR), the dopaminergic neurons of the ventral tegmental area (VTA), and the noradrenergic neurons of the locus coeruleus (LC). These neurons are silent during REM. OX_1- and OX_2-containing orexinergic neurons of the lateral hypothalamus decrease their firing activity during NREM and REM. The histaminergic H_1-containing neurons of the tuberomammillary nucleus (TMN) decrease their firing activity during sleep. During wakefulness, these arousal centers each send widespread ascending projections to the cerebral cortex, stimulating cortical desynchronization with high-frequency gamma and low-frequency theta rhythmic activity. Bottom left, black: The receptors likely responsible for the switch from wakefulness to NREM sleep are MT_1 and MT_2 receptors expressed in suprachiasmatic neurons, which receive inputs directly from the retinohypothalamic tract (RHT), influenced by light and external stimuli. The transition from NREM and REM is controlled by the ventrolateral periaqueductal gray area (vlPAG), containing melatonin MT_2 receptors, GABA, and glutamate receptors. Top right, red: During NREM sleep, two nuclei are particularly active: the reticular thalamus (RT), containing melatonin MT_2 and GABA receptors, which is responsible for thalamocortical input to the prefrontal cortex (showing synchronized activity during NREM), and the ventrolateral preoptic area (vlPAG), containing GABA and galanin receptors, which inhibits noradrenergic, serotonergic, cholinergic, histaminergic, and hypocretinergic neurons. These nuclei play a role in the "reciprocal inhibitory" model of the sleep-wake switch. Bottom right, blue: The vlPAG is a putative "REM ON" nucleus, switching the brain to the REM sleep mode. During REM, the sublateral nucleus (SLD), the basal forebrain (BF), and the lateral tegmentum/ pedunculopontine tegmentum (LDT/PPT, rich in acetylcholine receptors) and the ventromedial medulla (VM) neurons become particularly active. Note that the basal forebrain is active in REM and wakefulness and inhibited during NREM.

13-fold higher for patients ≥75 years old compared with patients <75 years old (European Medicines Agency, 2016). Smoking, oral contraceptive pills, and the presence of hepatic impairment likewise significantly affect agomelatine's pharmacokinetics. The metabolism of agomelatine occurs mainly via hepatic CYP1A2, and CYP1A2 polymorphisms have been shown to significantly affect the pharmacokinetics the drug (Song et al., 2014).

3. Indications. Agomelatine is approved for use in the European Union and Canada for the treatment of major depressive disorder (MDD) but not approved in the United States (Sansone and Sansone, 2011). Clinical studies examining the hypnotic effects of agomelatine are detailed in Table 3.

4. Results in Insomnia Disorder. No studies of agomelatine as a treatment of insomnia disorder were found.

5. Other Results. The studies of agomelatine were conducted in people diagnosed with major depressive disorder. In a 6-week randomized, double-blinded comparison study ($N = 332$) in people diagnosed with major depressive disorder (Kasper et al., 2010), agomelatine was significantly superior to sertraline at improving sleep latency ($P < 0.001$) and sleep efficiency ($P < 0.001$); furthermore, symptoms of depression ($P < 0.05$) and anxiety ($P < 0.05$) improved significantly more with agomelatine than with sertraline. Another randomized, double-blinded study comparing agomelatine and escitalopram ($N = 138$) found that agomelatine resulted in a greater reduction in sleep latency than escitalopram from week 2 onward (Quera-Salva et al., 2011). Moreover, although escitalopram reduced the number of sleep cycles relative to baseline, agomelatine preserved the number of sleep cycles. Finally, a review that pooled the results from three randomized studies ($N = 721$) comparing agomelatine to SSRIs or venlafaxine (Quera-Salva et al., 2010) established that agomelatine increases SWS, improves sleep efficiency, and resynchronizes SWS to the first sleep cycle of the night in patients with major depressive disorder while not changing the amount or latency of REM sleep.

6. Conclusion. A summary of the effects of agomelatine on sleep architecture is presented in Table 2. There is good evidence that agomelatine is superior to other antidepressants at reducing sleep latency in patients with major depressive disorder based on one review and two randomized, double-blind comparison studies (Kasper et al., 2010; Quera-Salva et al., 2010, 2011). Based on these same studies, the evidence is weak for the use of agomelatine in insomnia.

B. Prolonged-Release Melatonin

1. Indications. Melatonin is FDA-approved as a dietary supplement with no dosage restriction. In Europe, prolonged-release melatonin 2 mg/day is approved for the treatment of insomnia in elderly patients.

PRM is a new option in the treatment arsenal for insomnia. It is targeted specifically toward older adults, potentially because endogenous melatonin production declines with age and PRM mimics the pharmacokinetics of endogenous melatonin (Lemoine and Zisapel, 2012). However, a 3-week RCT found that the effects of PRM in patients with low endogenous melatonin among all ages did not differ from placebo (Wade et al., 2010); in contrast, PRM significantly reduced sleep latency compared with the placebo in elderly patients irrespective of melatonin levels (−19.1 vs. −1.7 minutes). This finding supports the idea that PRM has targeted efficacy specifically among the elderly, the same group of patients for whom benzodiazepine treatment is discouraged due to the increased risk of falls, accidents, and cognitive impairment ("What's Wrong," 2004). Clinical studies examining the hypnotic effects of PRM are detailed in Table 4.

2. Pharmacokinetics. Absorption of orally ingested melatonin is complete in healthy adults, although it may be decreased by up to 50% in the elderly (European Medicines Agency, 2017). Melatonin has linear pharmacokinetics over the dosage range of 2–8 mg, although bioavailability is only about 15%, and the rate of prolonged-release melatonin absorption is affected by food: the presence of food delayed the absorption of prolonged-release melatonin, resulting in a later and lower peak plasma concentration in the fed state. The metabolism of melatonin is mainly mediated by CYP1A enzymes, although exogenous administration of melatonin does not induce these enzymes, even at supratherapeutic dosages (European Medicines Agency, 2017).

3. Results in Insomnia Disorder. Four RCTs and one open-label trial found PRM effective in the treatment of primary insomnia in the elderly. Only one RCT, the largest one ($N = 791$), included patients below 55 years of age; this study demonstrated that PRM was only effective in the subgroup of patients over 55 years old, validating its specific efficacy among the elderly but not other groups (Wade et al., 2010). Among the elderly in this study, PRM reduced subjective sleep latency compared with baseline by −19.1 versus −1.7 minutes for placebo.

4. Other Results. One RCT ($N = 80$) in patients with mild to moderate Alzheimer's disease with and without insomnia comorbidity found that patients treated with PRM had significantly superior cognitive performance during the trial; in contrast, PSQI scores did not significantly change in the study, although sleep efficiency was found significantly to improve in patients with and without comorbid insomnia (Wade et al., 2014).

5. Conclusion. A summary of the effects of PRM on sleep architecture is presented in Table 2. There is good evidence that PRM is effective in the treatment of insomnia disorder in adults over 55 years of age, based on four RCTs. There is also evidence that PRM is not effective in the treatment of primary insomnia in younger adults, based on one RCT (Wade et al., 2010).

C. Ramelteon

1. Mechanism of Action. Ramelteon is a potent and highly selective agonist at the MT_1 and MT_2 receptors

TABLE 3
Summary of studies assessing the effects of agomelatine (AGM) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Kasper et al. (2010)	18–60	Major depressive disorder	6-wk randomized, double-blind comparison study of AGM 25-50 mg/day vs. sertraline 50–100 mg/day. N = 332.	AGM was significantly superior to sertraline from week 1 to week 6 by improvement in SOL, $P < 0.001$, and improvement in SE, $P < 0.001$. Depressive and anxiety symptoms also improved more with AGM than sertraline.	Incidence of treatment-emergency adverse events (AEs) was 48.0% for AGM and 49.1% for sertraline. Most common reported AEs in both groups were headache, dry mouth, and diarrhea. Fatigue more common in AGM group and hyperhydrosis more common in sertraline group.	AGM is effective at reducing symptoms of insomnia in depressed patients and significantly superior to sertraline.
Quera-Salva et al. (2010)	NS	Major depressive disorder	Review with pooled analysis of three randomized studies at end-point or after 6 or 8 wk of treatment with AGM 25/50 mg/day vs. SSRIs or venlafaxine. N = 721.	HAM-D Item 4, early insomnia: AGM 25/50 mg/day reduced score from 1.4 ± 0.7 to 0.5 ± 0.7 at endpoint vs. placebo reduced score from 1.4 ± 0.7 to 0.7 ± 0.8, $P < 0.001$. For HAM-D Item 4, middle insomnia: comparison between placebo and AGM yielded $P = 0.015$. For HAM-D Item 5, late insomnia: comparison between placebo and AGM yielded $P = 0.006$.	Not analyzed.	AGM is effective at reducing symptoms of insomnia in depressed patients and superior to other antidepressants.
Quera-Salva et al. (2011)	19–60	Major depressive disorder	6-wk with optional 18-wk extension period randomized, double-blind comparison study of AGM 25–50 mg/day vs. escitalopram 10–20 mg/day. N = 138.	AGM significantly reduced SOL from week 2 onwards compared with escitalopram: estimated difference (minute) at week 2 was −19 [−30, −9], $P < 0.001$; at week 6 was −14 [−24, −5], $P = 0.013$; at week 24 was −18 [−33, −3], $P < 0.0001$. TST was increased with AGM but decreased with escitalopram relative to baseline. SE was stable with AGM but decreased with escitalopram. Number of sleep cycles was stable with AGM but decreased with escitalopram.	Withdrawals due to AEs were less frequent with agomelatine (3%) than escitalopram (8%). Proportion of patients reporting at least one AE was lower with agomelatine than escitalopram (66% vs. 82%, $P = 0.038$). Headache, nasopharyngitis, and nausea were the most common AEs in both groups.	AGM is effective at reducing symptoms of insomnia in depressed patients and superior to escitalopram.

TABLE 4
Summary of studies assessing the effects of the prolonged-release melatonin formulation (PRM) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Arbon et al. (2015)	55–64	Healthy participants	Double-blind, placebo-controlled, four-way crossover trial. PRM 2 mg vs. temazepam 20 mg vs. zolpidem (10 mg) vs. placebo. $N = 16$	PRM has minor effects on stage N3 in comparison with those of temazepam and zolpidem.	10 adverse events of mild intensity due to PRM. The most common reported were gastrointestinal disorders (constipation, dry mouth, flatulence, and nausea), nervous system disorders (balance disorder, somnolence, and headache), and general disorders (fatigue and feeling hot).	PRM does not significantly affect sleep parameters in elderly.
Dolev (2011)	*See Mirtazapine section*					
Lemoine et al. (2007)	55+	Primary insomnia	2-wk single-blind placebo run-in period followed by a 3-wk RCT treatment period. PRM 2 mg/day vs. placebo. $N = 170$.	PRM improved QOS measured by LSEQ (-22.5 vs. -16.5, $P = 0.047$).	Nine patients in each treatment group reported AEs. The most common reported AEs were mild. Diarrhea occurred in one patient receiving PRM and one patient receiving placebo.	PRM is effective at reducing symptoms of insomnia in the elderly.
Lemoine et al. (2011)	20–80	Primary insomnia	6–12 mo open-label continuation trial. PRM 2 mg/day. $N = 244$.	The mean (+S.E.M.) percentage of nights per week scored by the patients as "good" or "very good" increased progressively with treatment duration. At the plateau level, 54%–56% of nights per week were scored as "good" or "very good" (i.e., 3.8 nights/wk) compared with 26% (i.e., 1.8 nights/wk) at baseline ($P < 0.001$), which was maintained throughout trial.	PRM discontinuation even after 12 mo was not associated with AEs, withdrawal symptoms, or suppression of endogenous melatonin production. Most common reported events were pharyngitis (12.4%) and back pain (11.8%).	PRM is effective at reducing symptoms of insomnia as long-term treatment.
Lemoine and Zisapel (2012)	55+	Primary insomnia	Post hoc analysis of pooled antihypertensive drug-treated subpopulations from four randomized, double-blind trials of PRM and placebo for 3 wk. $N = 589$.	By the end of the 6-mo treatment period, means subjective improvement in patients' evaluated SOL was significantly higher with PRM (25.89 minutes) than with placebo (7.54 minutes) $P = 0.02$.	Rate of AEs normalized per 100 patient-weeks was lower for PRM (3.66) than for placebo (8.53).	PRM is efficacious and safe in primary insomnia patients treated with antihypertensive drugs
Luthringer et al. (2009)	55+	Primary insomnia	2-wk single-blind placebo run-in followed by 3-wk RCT of PRM 2 mg/day for 3 wk followed by a 3-wk withdrawal period. $N = 40$	PRM group had significantly shorter SOL (9 min; $P = 0.02$) compared with the placebo group and scored significantly better in the Critical Flicker Fusion Test ($P = 0.008$) without negatively affecting sleep structure and architecture. Half of the patients reported substantial improvement in QOS at home with PRM compared with 15% with placebo ($P = 0.018$). No rebound effects were observed during withdrawal	AEs were reported by 11 patients in each treatment group. The most common AE was headache, reported by four patients in the PRM group and three in the placebo group. No significant difference in the incidence of AEs.	PRM was effective in reducing symptoms of insomnia.

(*continued*)

TABLE 4—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Otmani et al. (2008)	55+	Healthy participants	RCT crossover study. PRM 2 mg, zolpidem 10 mg, PRM + zolpidem vs. placebo. Effects on psychomotor functions, memory recall, and driving skills were assessed at 1, 4 h and morning following administration. $N = 16$.	A main "treatment" effect was found for all variables ($P < 0.05$) Zolpidem significantly increased sedation compared with placebo at 1 hour ($P = 0.0011$, $P < 0.0001$, respectively) and 4 hours postdosing ($P < 0.0001$ for both) and compared with PRM at 1 hour ($P = 0.03$, $P < 0.0001$, respectively) and 4 hour ($P = 0.015$ for both).	N/A	PRM does not have significant cognitive adverse effects in the elderly.
Wade et al. (2007)	55–80	Primary insomnia	2-wk single-blind placebo run-in period followed by a 3-wk RCT treatment period. PRM 2 mg/day vs. placebo. $N = 354$.	PRM improved quality of sleep measured by LSEQ (−22.5 vs. −16.5, $P = 0.047$).	24% and 21% of patients in the respective PRM and placebo groups reported AEs. Most commonly reported effects were nasopharyngitis and headache or migraine.	PRM is effective at reducing symptoms of insomnia in the elderly.
Wade et al. (2010)	18–80	Primary insomnia	2-wk single-blind placebo run-in period followed by 3-wk RCT of PRM 2 mg/day vs. placebo; 26-wk extension study with 2 wk of single-blind placebo run-out. $N = 791$	PRM in patients with low endogenous melatonin regardless of age did not improve SOL compared with placebo, whereas PRM significantly reduced SOL compared with placebo in elderly patients regardless of melatonin levels (−19.1 vs. −1.7 min; $P = 0.002$).	AE rates were similar between PRM and placebo groups. 34.5% and 35.9% of respective PRM- and placebo-treated patients reported any AE during the treatment period. In extension period, 73.8% and 76.8% of PRM- and placebo-treated subjects reported any AE. Most common events were nasopharyngitis, arthralgia, diarrhea, respiratory tract infections, and headache.	PRM is effective at reducing symptoms of insomnia in the elderly. The results demonstrate short- and long-term efficacy and safety of PRM in elderly insomnia patients. Low melatonin production regardless of age is not useful in predicting responses to melatonin therapy in insomnia.
Wade et al. (2014)	52–85	Mild to moderate Alzheimer's disease, with and without insomnia comorbidity	2-wk single-blind placebo run-in followed by 24-wk RCT and 2-wk placebo run-out period. PRM 2 mg/day vs. placebo. $N = 80$.	Patients treated with PRM (24 wk) had significantly better cognitive performance than those treated with placebo, as measured by the IADL ($P = 0.004$) and MMSE ($P = 0.044$). Mean ADAS-Cog did not differ between the groups. The PSQI global score improved in PRM (−1.62 [2.74], $P = 0.004$) but not placebo group (0.74 [2.52], $P = 0.139$)	AE rates were similar between PRM and placebo groups. 82.1% of PRM patients reported AEs vs. 67.6% of placebo-treated patients.	Add-on PRM has positive effects on cognitive functioning and sleep maintenance in AD patients compared with placebo, particularly in those with insomnia comorbidity.

with an affinity 3–16 times higher than that of melatonin (Kato et al., 2005). Its affinity for MT_2 is eight times lower than its affinity for MT_1. This binding profile distinguishes ramelteon from melatonin and tasimelteon, which both display more affinity for the MT_1 receptor than the MT_2 receptor (Lavedan et al., 2015). The hypnotic effect of ramelteon is mediated by its potent, long-lasting agonism of the melatonin receptors, because it does not exhibit affinity for benzodiazepine receptors, dopamine receptors, opiate receptors, ion channels, and does not affect the activity of various enzymes (Kato et al., 2005) (Table 1). While studies in rats and monkeys confirm that ramelteon reduces time to sleep onset without affecting total sleep time (Yukuhiro et al., 2004; Fisher et al., 2008), ramelteon increases total sleep time in cats (Miyamoto et al., 2004).

2. Indications. Ramelteon is FDA-approved for the treatment of insomnia characterized by difficulty with sleep onset (US FDA, 2010a). Notably, the European Medicines Agency initially rejected Takeda Pharmaceutical Company's application (filed in March 2007) for lack of efficacy. Later, in September 2008, the company withdrew their Marketing Authorization Application to the Committee for Medicinal Products for Human Use (CHMP). The CHMP was concerned that the company had not demonstrated the effectiveness of ramelteon, because only one aspect of insomnia, the time to fall asleep, had been assessed in the trials (European Medicines Agency, 2008b). Furthermore, only one of the three studies that had been carried out in the natural setting found a significant difference in the time taken to fall asleep between patients taking ramelteon and those taking placebo, and this difference was considered too small to be clinically relevant. When other aspects of sleep were considered, ramelteon did not have any effect (Kuriyama et al., 2014). The CHMP was also concerned that Takeda had not demonstrated the long-term effectiveness of ramelteon (European Medicines Agency, 2008b). Clinical studies examining the hypnotic effects of ramelteon are detailed in Table 5.

3. Pharmacokinetics. At a dose range of 4–64 mg, ramelteon undergoes rapid, high first-pass metabolism and exhibits linear pharmacokinetics (US FDA, 2010a). However, the drug shows substantial intersubject variability in maximal serum concentration and area under the concentration curve. Median peak concentration occurs at about 0.75 hours after fasted oral administration. Although total absorption is at least 84%, absolute bioavailability is only 1.8% because of extensive first-pass metabolism (US FDA, 2010a). It has a half-life of about 1–2.6 hours. CYP1A2 is the major liver enzyme involved in the hepatic metabolism of ramelteon, although CYP2C and CYP3A4 are also involved to a lesser degree: the drug is extensively transformed to its hydroxylated M-II metabolite, with serum AUC values that average approximately 30 times those of the parent drug (Greenblatt et al., 2007). It has been argued that M-II, with its longer half-life and greater systemic exposure, may contribute significantly to the hypnotic effect of ramelteon: M-II has been shown to bind to human MT_1 and MT_2 receptors, although with lower affinity (K_i: 114 and 566 pmol/l for MT_1 and MT_2, respectively) (Nishiyama et al., 2014). Taking ramelteon with a high-fat meal changes its pharmacokinetics; the area under the concentration curve for a single 16 mg dose is 31% higher, whereas maximal concentration is 22% lower than when administered in a fasted state (US FDA, 2010b). For this reason, the US FDA does not recommend taking ramelteon after a high-fat meal. Moreover, clearance is significantly reduced in the elderly,

4. Results in Insomnia Disorder. Two meta-analyses found ramelteon effective at reducing subjective sleep latency time in primary insomnia (Liu and Wang, 2012; Kuriyama et al., 2014). The first study analyzed 4055 patients (Liu and Wang, 2012) and the second analyzed 5812 patients (Kuriyama et al., 2014). One, a pooled analysis of four trials comparing ramelteon to placebo, found that active treatment reduced subjective sleep latency by −4.22 minutes, 95% confidence interval −5.66 to −2.77 minutes ($P < 0.00001$) (Liu and Wang, 2012). The other had similar results for subjective sleep latency reduction, although it pooled results from 12 studies: −4.30 minutes, 95% confidence interval −7.01 to −1.58 minutes ($Q = 23.64$; df = 11) (Kuriyama et al., 2014). However, it did not find that ramelteon increased total sleep time significantly more than placebo (Kuriyama et al., 2014).

5. Conclusion. A summary of the effects of ramelteon on sleep architecture is presented in Table 2. There is strong evidence that ramelteon is effective in the treatment of insomnia disorder characterized by difficulty with sleep onset, based on two meta-analyses (Liu and Wang, 2012; Kuriyama et al., 2014).

D. Tasimelteon

1. Mechanism of Action. Tasimelteon displays comparable potency to melatonin at the MT_1 receptor, whereas its affinity for MT_2 is 2.1–4.4 times greater than its affinity for MT_1 (Lavedan et al., 2015). Its agonism at these receptors is selective, as it lacks any other significant interactions with receptors or enzymes (Table 1).

2. Indications. Tasimelteon is the first FDA-approved treatment of non-24-hour sleep-wake disorder (non-24), for which it was granted orphan drug status. Initially, Vanda Pharmaceuticals evaluated the efficacy of tasimelteon in the treatment of insomnia in phase II and phase III studies (Vanda Pharmaceuticals Inc., 2008; Feeney et al., 2009), but the compound has only received regulatory approval for the treatment of non-24. Clinical studies examining the hypnotic effects of ramelteon are detailed in Table 6.

3. Pharmacokinetics. The pharmacokinetics of tasimelteon is linear over dose ranges from 3 to 300 mg, with an absolute oral bioavailability of 38.3% and a mean half-life of

TABLE 5
Summary of studies assessing the effects of ramelteon (RMT) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Erman et al. (2006)	18–64	Chronic primary insomnia	Five-period crossover RCT. RMT 4 vs. 8 vs. 16 vs. 32 mg/day vs. placebo. $N = 107$.	PSG LPS (minute) was 37.7 for placebo vs. 24.0 for RMT 4 mg/day, $P < 0.001$, vs. 24.3 for RMT 8 mg/day, $P < 0.001$, vs. 24.0 for RMT 16 mg/day, $P < 0.001$, vs. 22.9 for RMT 32 mg/day, $P < 0.001$. $P < 0.001$ for overall effect.	No difference in number or type of AEs between active treatment and placebo group.	RMT is effective at reducing symptoms of insomnia.
Gooneratne et al. (2010)	≤60	Obstructive sleep apnea	4-wk RCT. RMT 8 mg/day vs. placebo. $N = 21$.	Objective polysomnographic SOL (minute) was 20.4 ± 23.2 at baseline in the RMT group and 9.7 ± 10.3 after treatment. In the placebo group, objective SOL was 16.6 ± 17.5 at baseline and 34.4 ± 30.7 after treatment. For between groups comparison: $P = 0.008$. Subjective SOL was not significantly improved.	Four AEs occurred in RMT arm and two in placebo arm; none judged related to treatment.	RMT may be effective at reducing symptoms of insomnia in older adults.
Kohsaka et al. (2011)	20–65	Chronic primary insomnia	Crossover RCT (five periods of 2 nights each). RMT 4 vs. 8 vs. 16 vs. 32 mg/day vs. placebo. $N = 65$.	LPS (minute) was 29.02 ± 28.55 for RMT 4 mg/day, 22.12 ± 18.16 for RMT 8 mg/day, 28.17 ± 29.40 for RMT 16 mg/day, 24.37 ± 32.79 for RMT 32 mg/day, and 35.27 ± 40.68 for placebo. Differences between treatment and placebo were only significant for RMT 8 and 32 mg/day. However, the linear P value trend was: $P = 0.0046$.	The number of patients with an AE was higher in the 16 and 32 mg/day than with placebo and the 4 and 8 mg/day doses. The most common AEs were somnolence, headache, malaise, and dizziness.	RMT 8 and 32 mg/day are effective at reducing symptoms of insomnia.
Kuriyama et al. (2014)	18–93	Chronic, primary, or psychophysiological insomnia; bipolar disorder; insomnia associated with obstructive sleep apnea	Systematic review and meta-analysis of placebo-controlled RCTs. $N = 5812$.	RMT was significantly associated with reduced subjective SOL and improved QOS. It was not associated with increased subjective total sleep time.	Only significant AE was somnolence. No difference in occurrence of other AEs between RMT and placebo.	RMT is effective at reducing symptoms of insomnia.
Liu and Wang (2012)	18 and over	DSM-IV primary chronic insomnia	Systematic review and meta-analysis of placebo-controlled RCTs. $N = 4055$	Significant improvements in self-reported and polysomnographic SOL, TST, latency to REM. No improvement in percentage of REM.	RMT was not associated with a high risk ratio of any frequent AEs compared with placebo. However, there were significantly more subjective reports of at least one AE with RMT.	RMT is effective at reducing symptoms of insomnia.
Mayer et al. (2009)	18–79	Chronic primary insomnia	6-mo RCT. RMT 8 mg/day vs. placebo. $N = 451$.	RMT consistently reduced LPS compared with baseline and compared with placebo as measured by objective polysomnography. RMT reduced LPS (minute) from 70.75 at baseline to 32.02 at week 1. Similar effects were observed at each follow up.	Incidence of AEs was similar between RMT (51.8%) and placebo (50.7%) groups. Eight patients in RMT and 10 patients in placebo discontinued due to an AE. Leukopenia occurred in one RMT-treated subject and was judged as possibly treatment related.	RMT is effective at reducing symptoms of insomnia over the course of 6 mo.

(*continued*)

TABLE 5—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
McElroy et al. (2011)	18–65	Bipolar I disorder	8-wk RCT. 8 mg/day RMT vs. placebo. $N = 21$.	RMT and placebo and similar rates of reduction in symptoms of insomnia, mania, and global severity of illness. RMT was associated with improved depressive symptoms. Pittsburgh Insomnia Rating Scale total score difference from baseline to final visit: placebo, −69.3 vs. RMT, −54.2, $P = 0.46$.	One patient of 21 who were randomized withdrew due to sedation (RMT group). No participant experienced a serious AE. Small sample size limits ability to detect meaningful differences in the occurrence of AEs.	RMT may not be effective at reducing symptoms of insomnia in bipolar I disorder.
NCT#00755495	18–80	Primary insomnia by DSM-IV-TR	5-wk RCT. RMT 8 mg/day + doxepin 3 mg/day vs. RMT 8 mg/day vs. doxepin 3 mg/day vs. placebo. $N = 472$.	RMT 8 mg/day + doxepin 3 mg/day was significantly superior to placebo at reducing LPS at week 1, $P < 0.001$. However, at week 3, $P = 0.400$, and at week 5, $P = 0.122$. RMT 8 mg/day + doxepin 3 mg/d was significantly superior to placebo at increasing TST at all time points: $P < 0.001$ at week 1, $P = 0.017$ at week 3, and 0.036 and week 5.	The rates of AEs were similar among all treatment groups: 28.1% of RMT + doxepin, 30.8% for doxepin, 35.9% for RMT, 36.6% for placebo. Most reported AEs were somnolence (4.9%) and headache (4.5%), with somnolence occurring with the greatest incidence in the RMT + doxepin group (8.8%).	RMT + doxepin is effective at reducing symptoms of insomnia. Subjective sleep quality improved more with RMT + doxepin than with RMT alone over 5 wk of treatment.
Roth et al. (2006)	64–93	Primary insomnia	35-night RCT. RMT 4 mg/day vs. 8 mg/day vs. placebo. $N = 829$.	LPS (minute) at week 1 was 70.2 for RMT 4 mg/day vs. 78.5 min for placebo, $P = 0.008$; it was 70.2 for RMT 8 mg/day vs. 78.5 for placebo, $P = 0.008$. RMT also significantly increased TST and rebound insomnia or withdrawal effects were not observed following discontinuation.	Incidence of AEs was similar among all treatment groups. Incidence of any AE: 51.5% of placebo group, 54.8% of RMT 4 mg/day, 58.0% of RMT 8 mg/day.	RMT is effective at reducing symptoms of insomnia.
Roth et al. (2007)	65–83	Chronic primary insomnia	9-wk, three-period crossover RCT trial with treatment administered for 2 nights per treatment. RMT 4 vs. 8 mg/day vs. placebo. $N = 100$.	SOL (minute) was 28.7 for RMT 4 mg/day vs. 38.4 for placebo, $P < 0.001$; 30.8 for RMT 8 mg/day vs. 38.4 for placebo, $P = 0.005$. TST and SE were also significantly improved.	Incidence of AEs considered treatment-related was placebo 7%, RMT 4 mg/day 11%, and RMT 8 mg/day 5%. No evidence of next-day psychomotor or cognitive effects.	RMT is effective at reducing symptoms of insomnia.
Uchimura et al. (2011)	Mean: 48.8; S.D.: 17.2	Chronic insomnia	RCT. RMT 4 vs. 8 mg/day vs. placebo for 2 wk followed by dose escalation to 8 vs. 16 vs. 4 mg/day, respectively, for 2 wk. $N = 1143$.	LS mean weekly subjective SOL (minute) at week 1: RMT 4 mg/day was not significantly superior to placebo, $P = 0.9315$. RMT 8 mg/day was not significantly superior to placebo, $P = 0.0905$.	42.1% in the placebo/4 mg/day group, 42.5% in the 4/8 mg/day group and 41.8% in the 8/16 mg/day group reported at least one treatment-emergent AE The incidences of AEs among the treatment groups were comparable, and no dose–response relationships were observed.	RMT may not be effective at reducing symptoms of insomnia.

(*continued*)

TABLE 5—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Uchiyama et al. (2011)	20–85	Chronic insomnia	4-wk RCT. RMT 8 mg/day vs. placebo for 2 wk followed by 2-wk placebo run-out period to monitor rebound insomnia. N = 987.	RMT was significantly superior to placebo at reducing SOL at week 1 but insignificantly superior to placebo at week 2. LS mean (in minute) for RMT was 61.15 ± 0.97 at week 1 vs. 65.69 ± 0.97 for placebo.	No evidence of rebound insomnia. 2.7% of RMT group and 2.3% of placebo group discontinued due to AEs. The most common reason in both groups was nasopharyngitis. One serious adverse effect occurred in RMT group, a road accident >15 h after taking drug.	RMT is effective at reducing symptoms of insomnia after 1 wk of treatment.
Wang-Weigand et al. (2011)	18–64	Chronic insomnia	3-wk RCT. RMT 8 mg/day vs. placebo. N = 556.	For mean subjective SOL relative to placebo: week 1 - reduction of 4.1 min, P = 0.088. Week 2: reduction of 2.8 min, P = 0.258. Week 3: reduction of 4.9 min, P = 0.060. No significant difference from placebo.	Somnolence occurred in 1.8% of placebo group and 4.4% of RMT group. The proportion of subjects with any treatment-related AEs was similar between groups (placebo 15.4%, ramelteon 16.5%).	RMT 8 mg/day may not be effective at reducing symptoms of insomnia.
Zammit et al. (2007)	18–64	Primary insomnia	5-wk RCT. RMT 8 vs. 16 mg/day vs. placebo. N = 405.	LPS (minute) at week 1 was 32.2 for RMT 8 mg/day vs. 28.9 for RMT 16 mg/day vs. 47.9 for placebo, $P < 0.001$; significant improvements were maintained at weeks 3 and 5.	No evidence of next-day pharmacologic residual effects. No evidence of rebound insomnia following discontinuation of RMT. Most common AE in all groups was headache.	RMT is effective at reducing symptoms of insomnia.
Zammit et al. (2009)	≥65	Insomnia	Three-way crossover RCT. RMT 8 mg/day vs. zolpidem 10 mg/day vs. placebo. N = 33.	While zolpidem significantly impaired performance on the sensory organization test, turn time, and turn sway ($P < 0.001$ for all), RMT did not produce any differences from placebo. Immediate recall declined significantly with zolpidem (P = 0.002) while it was similar to placebo for RMT.	N/A	RMT did not impair middle-of-the-night balance, mobility, or memory in older adults relative to placebo

1.3 ± 0.4 hours (US FDA, 2014b). Like for ramelteon, taking tasimelteon with a high-fat meal lowers C_{max} (by 44%) and delays T_{max} (by 1.75 hours) compared with the fasted state. For this reason, the FDA recommends that the drug not be taken with food. CYP1A2 and CYP3A4 are the major isoenzymes associated with its hepatic metabolism, and major metabolites have 13-fold or less activity at melatonin receptors (US FDA, 2014b). Exposure to tasimelteon increases approximately twofold in the elderly compared with nonelderly adults and in women approximately 20%–30% compared with men. Smokers had approximately 40% lower exposure to tasimelteon than nonsmokers.

4. Results in Healthy Volunteers. Two short RCTs of tasimelteon in healthy volunteers have been published: a phase II RCT and a phase III RCT (again in healthy volunteers) of the drug as a treatment of transient insomnia induced by shifted sleep (Rajaratnam et al., 2009). In the phase II trial, the individuals were monitored for seven nights: three at baseline, three after a 5-hour advance of the sleep-wake schedule, and one night after treatment. In the phase II RCT, tasimelteon reduced sleep latency and increased sleep efficiency relative to placebo and shifted the plasma melatonin rhythm to an earlier hour. The phase III study had similar positive results.

5. Results in Insomnia Disorder. There were no published studies of tasimelteon in patients diagnosed with insomnia disorder. However, one clinical trial in patients with primary insomnia (NCT#00548340), which was published only as an abstract, found a significant mean change in latency to persistent sleep [standard error]: 45.0 [2.965] for tasimelteon 20 mg/day versus 46.4 [2.954] for tasimelteon 50 mg/day versus 28.3 [3.020] for placebo (Vanda Pharmaceuticals Inc., 2014).

6. Results in Other Conditions. Other trials were conducted in patients diagnosed with non-24 sleep-wake disorder (Lockley et al., 2015), for which tasimelteon has gained FDA approval as an orphan drug (Dhillon and Clarke, 2014). The investigators found that tasimelteon significantly improved entrainment.

7. Conclusion. A summary of the effects of tasimelteon on sleep architecture is presented in Table 2. There is poor-quality evidence for the use of tasimelteon in the treatment of insomnia disorder, based on two studies in healthy volunteers (Rajaratnam et al., 2009).

V. Orexin Receptor Antagonist Drugs

A. Suvorexant

1. Mechanism of Action. Suvorexant's effect as a hypnotic is attributable to its selective antagonism of the orexin receptors OX1R and OX2R (Winrow et al., 2011; Yin et al., 2016) (Table 1). In vitro assay panels demonstrate suvorexant's selectivity for the orexin receptors over 170 known receptors and enzymes (Cox et al., 2010). In mice, suvorexant has been shown to selectively increase REM sleep in the first 4 hours after dosing (Hoyer et al., 2013).

2. Indications. Suvorexant is FDA approved for the treatment of insomnia characterized by difficulty with sleep onset and/or sleep maintenance at the doses of 5, 10, 15, and 20 mg/day but not the higher doses studied in the clinical trials (US FDA, 2014a). The FDA chose not to approve suvorexant at the 30 or 40 mg/day doses studied in the phase III trials because of safety concerns, particularly next-day driving impairment at doses of 20 mg/d and higher (US FDA, 2014a). There were also a few reports of sleep paralysis and hallucinations, unconscious nighttime behaviors, and narcolepsy-like events among drug-treated subjects. Clinical studies examining the hypnotic effects of suvorexant are detailed in Table 7.

3. Pharmacokinetics. Exposure to suvorexant does not increase linearly over the dosage range 10–80 mg because the drug is absorbed less at higher doses (US FDA, 2014a). The mean bioavailability of suvorexant 10 mg is 82% and ingestion of the drug with food does not meaningfully affect AUC or C_{max} but does delay T_{max} by approximately 1.5 hours. Steady-state pharmacokinetics are achieved in 3 days, and the mean half-life of the drug is 12 hours (95% confidence interval: 12–13). Exposure to suvorexant is higher in women than in men, with AUC increased 17% and C_{max} increased 9%, for suvorexant 40 mg.

4. Results in Insomnia Disorder. There are two systematic reviews of suvorexant as a treatment of primary insomnia (Citrome, 2014; Kishi et al., 2015). Although both reviews analyze the same four phase II and phase III trials in insomnia patients, one of them differs from the other by following PRISMA reporting guidelines (Kishi et al., 2015). Both systematic reviews analyzed the same four phase II and phase III RCTs and came to similar conclusions: that suvorexant was safe and effective for the treatment of insomnia. Suvorexant improved subjective total sleep time (weighted mean difference = −20.16, 95% confidence interval = −25.01 to −15.30, 1889 patients, three trials) and subjective time to sleep onset (weighted mean difference = −7.62, 95% confidence interval = −11.03 to −4.21, 1889 patients, three trials) (Kishi et al., 2015).

Subgroup analysis of approved (15 and 20 mg/day) versus unapproved (30 or 40 mg/day) found that for efficacy, the number needed to treat values versus placebo of suvorexant 40 and 30 mg/day and that of the 20 and 15 mg/day doses were the same: 8 (Citrome, 2014). However, for adverse effects, there were number needed to harm values versus placebo of 13 for the higher doses and 28 for the lower doses, indicating that the lower doses are better tolerated. Although the other systematic review did not specifically analyze approved versus unapproved doses, the authors performed an analysis in which they excluded the higher doses from the primary outcomes and found that suvorexant remained superior to placebo in subjective total sleep time and subjective time to sleep onset at 1 month (Kishi et al., 2015). Suvorexant was found to have an efficacy similar to the benzodiazepines, ramelteon, and

TABLE 6
Summary of studies assessing the effects of tasimelteon (TMT) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Johnsa and Neville (2014)	Heterogeneous	Heterogeneous	Review of four RCTs.	In one phase II trial, significant shifts in circadian rhythm were observed only for TMT 100 mg/day. In a phase III trial, LPS was significantly improved in the TMT group relative to placebo. The SET and RESET trials both found TMT to significantly improve entrainment in non-24-hour sleep-wake disorder patients.	Frequency and severity of AEs were similar across treatment groups. Most common AEs were somnolence and headache.	TMT is effective at reducing symptoms of non-24-hour sleep-wake disorder.
Lockley et al. (2015)	18–75	Total blindness with non-24-hour sleep-wake disorder	Two RCTs, SET (26 wk, $N = 84$) and RESET (19 wk, $N = 20$). TMT 20 mg/day vs. placebo.	TMT significantly improved entrainment, although the effect did not last after discontinuation.	No significant difference in the discontinuation rate due to AEs between the TMT (6%) and placebo (4%) groups. Headache and increased alanine aminotransferase occurred in more patients receiving TMT than placebo.	TMT is effective at reducing symptoms of non-24-hour sleep-wake disorder.
NCT#00548340	18–65	Primary insomnia	5-wk RCT. TMT 20 vs. 50 mg/day vs. placebo. $N = 321$.	Statistics were not conducted. Mean change in LPS [S.E.] was 45.0 [2.965] for TMT 20 mg/day, 46.4 [2.954] for TMT 50 mg/day, and 28.3 [3.020] for placebo. Mean change in TST was 51.4 [4.794], 52.0 [4.775], and 39.9 [4.882] for the same respective groups.	Most common AEs were nasopharyngitis and headache.	Statistics were not conducted.
Rajaratnam et al. (2009)	Phase II RCT: 18–50. Phase III RCT: 21–50.	Phase II RCT: healthy volunteers. Phase III RCT: healthy volunteers with induced transient insomnia	Two RCTs. Phase II RCT: TMT 10 vs. 20 vs. 50 vs. 100 mg/day vs. placebo. $N = 39$. Phase III RCT: TMT 20 vs. 50 vs. 100 mg/day vs. placebo. $N = 411$.	In the phase II RCT, TMT reduced SOL and increased SE compared with placebo. In the phase III study, TMT improved SOL, SE, and WASO. LPS was significantly reduced relative to placebo: in phase II study, TMT 10 mg/day, $P = 0.003$; 50 mg/day, $P = 0.019$; 100 mg/day, $P = 0.021$. In the phase III study, all doses of TMT, $P < 0.001$ for reducing LPS.	Rates of AEs were similar between TMT and placebo.	TMT is effective at reducing symptoms of insomnia in a model of circadian rhythm disorders.

TABLE 7
Summary of studies assessing the effects of suvorexant (SVX) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Citrome (2014)	18–87	Primary insomnia	Systematic review of four phase II and phase III RCTs.	LS mean difference from placebo in subjective TST at month 1 (minute): 18.4, $P < 0.001$ for SVX 15 or 20 mg; 22.7, $P < 0.001$ for SVX 30 or 40 mg. LS mean difference from placebo in SOL by polysomnography at month 1 (minute): −9.1, $P < 0.001$ for SVX 15 or 20 mg; −11.4, $P < 0.001$ for SVX 30 or 40 mg.	Rebound insomnia and withdrawal effects not observed after treatment discontinuation. Somnolence is the most common AE.	SVX is effective at reducing symptoms of insomnia. Higher doses are more effective but may have a higher risk of AEs.
Herring et al. (2012)	18–64	Primary insomnia by DSM-IV	4-wk crossover RCT. SVX 10 vs. 20 vs. 40 vs. 80 mg/day. $N = 254$.	Objectively-measured LPS (minute) at EOS was changed relative to placebo −2.3 [−12.2, 7.5] for 10 mg/day, −22.3 [−32.3, −12.3] for 20 mg/day, −3.8 [−13.8, 6.3] for 40 mg/day, −9.5 [−19.7, 0.7] for 80 mg/day. However, in general, more robust effects were observed for SVX 40 and 80 mg/day on subjective SOL, objective TST, and subjective QOS.	10 and 20 mg/day showed similar levels of adverse effects to placebo, while 40 and 80 mg/day had increased adverse effects. One patient receiving SVX 80 mg/day had a mild visual hallucination and discontinued. Most common AEs were somnolence, headache, and dizziness.	SVX is effective at reducing symptoms of insomnia. SVX 10 and 20 mg/day are better tolerated then 40 and 80 mg/day.
Herring et al. (2016)	nonelderly (18–64) and elderly (≥65)	Primary insomnia by DSM-IV-TR	Two 3-mo RCTs in elderly and non-elderly patients. SVX 40/30 mg/day vs. SVX 20/15 mg/day vs. placebo. $N = 1021$ in first RCT and $N = 1019$ in second RCT.	Subjective SOL (minute) difference between SVX 40/30 mg/day and placebo at month 3: −8.4 [−12.8, −4.0] in trial 1, −13.2 [−19.4, −7.0] in trial 2.	The most common AE that was increased for SVX vs. placebo was next-day somnolence.	SVX is effective at reducing symptoms of insomnia. SVX 40/30 mg/day was superior to placebo on almost all subjective and polysomnography end points in both trials; SVX 20/15 mg/day was superior to placebo on many subjective measures.
Kishi et al. (2015)	NS	Primary insomnia by DSM-IV	Systematic review and meta-analysis of four placebo-controlled RCTs. $N = 3076$.	Mean pooled (15 and 40 mg/day) difference between SVX and placebo in subjective TST at month 1 (minute): −20.16 [−25.01, −15.30]. Mean pooled (15 and 40 mg/day) difference between SVX and placebo in subjective TST at month 1 (minute): −7.62 [−11.03, −4.21].	Discontinuation due to all-cause, inefficacy, and intolerability did not differ between groups. SVX group had higher incidence of abnormal dreams, somnolence, excessive daytime sleepiness, fatigue, and dry mouth.	SVX is effective at reducing symptoms of insomnia.

(*continued*)

TABLE 7—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Michelson et al. (2014)	18+	Primary insomnia by DSM-IV-TR	Yearlong RCT with a subsequent 2-mo randomized discontinuation phase in which participants given placebo were switched to SVX and vice versa. SVX 40 mg/day for patients younger than 65, 30 mg/day for patients older than 65, or placebo. N = 781.	Change in subjective SOL (minute) at month 12 for SVX was −26.6 [−30.5, −22.7] vs. −17.0 [−22.6, −11.4] for placebo, P = 0.0055. Change in subjective TST (minute) at month 12 was 60.5 [54.0, 66.9] for SVX vs. 33.0 [23.7, 42.2] for placebo, $P < 0.0001$.	Most common AE, somnolence, reported for 13% of patients receiving SVX vs. 3% of those receiving placebo. Fatigue and dry mouth were also increased for SVX vs. placebo groups.	SVX is effective at reducing symptoms of insomnia. SVX is probably not associated with rebound insomnia during discontinuation after 1 yr of treatment.
Sun et al. (2013)	18–45	Healthy young men	Four-period crossover RCT followed by a fifth period to assess pharmacokinetics. SVX 10 vs. 50 vs. 100 mg/day N = 22 (completed 19).	SVX 50 and 100 mg decreased LPS and WASO and increased SE and TST.	All reported adverse events were mild. The most frequently reported adverse events were somnolence (20% in those receiving SVX 100 mg) and headache.	SVX is effective at promoting sleep in healthy subjects without known sleep impairments

sedating antidepressants at reducing symptoms of insomnia (Kishi et al., 2015).

5. Conclusion. A summary of the effects of suvorexant on sleep architecture is presented in Table 2. There is strong evidence that suvorexant is effective at reducing symptoms of insomnia disorder at doses 15–40 mg/day, based on two systematic reviews (Citrome, 2014; Kishi et al., 2015). Suvorexant exerts strong effects on increasing total sleep time. Lower doses may be preferred, per FDA guidelines, to minimize the risk of adverse effects.

VI. Antidepressant Drugs

Sedating antidepressants are commonly prescribed for insomnia: one analysis found that they were prescribed more often than the FDA-approved treatments for insomnia in 2002 (Walsh, 2004; McCall, 2016). Trazodone was the most commonly prescribed medication for insomnia in 2002, with 34% more prescriptions than the most commonly prescribed FDA-approved treatment (Walsh, 2004). In fact, there were 5.28 million prescriptions for antidepressants for insomnia and only 3.4 million prescriptions for FDA-approved hypnotics (Walsh, 2004).

A. Amitriptyline

1. Mechanism of Action. Amitriptyline is a tricyclic antidepressant with strong effects as a serotonergic reuptake inhibitor [SERT K_i (nM) = 3.13] (Vaishnavi et al., 2004) and moderate effects as a norepinephrine reuptake inhibitor [NET K_i (nM) = 22.4] (Tatsumi et al., 1997). Indeed, serotonergic-norepinephrine reuptake inhibitors lack hypnotic properties, and as thus, amitriptyline's hypnotic effects are attributable to its profile as an H_1 and H_2 receptor antagonist as well as a 5-HT_{2A} and 5-HT_{2C} antagonist. Main molecular targets of amitriptyline are summarized in Table 1.

2. Indications. Amitriptyline is FDA approved for the treatment of major depressive disorder (Alphapharm, 2012). Clinical studies examining the hypnotic effects of amitriptyline are detailed in Table 8.

3. Pharmacokinetics. Amitriptyline is well-absorbed with peak plasma concentrations occurring within 6 hours of oral administration (Alphapharm, 2012). The mean half-life of amitriptyline is 22.4 hours, whereas the mean half-life of its active metabolite nortriptyline is 26 hours. Amitriptyline is 96% bound to plasma proteins, and undergoes extensive first-pass metabolism in the liver to nortriptyline via *N*-demethylation mediated by CYP2C19 (Rudorfer and Potter, 1999). Other liver enzymes involved in its metabolism are CYP2D6 and CYP3A4 (Rudorfer and Potter, 1999). Genetic heterogeneity between patients affects the concentration of the drug in the body, particularly the ratio between amitriptyline and nortriptyline (Rudorfer and Potter, 1999).

4. Results in Insomnia Disorder. No studies of amitriptyline as a treatment of insomnia disorder were identified.

TABLE 8
Summary of studies assessing the effects of amitryptiline (AMT) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Hartmann and Cravens (1973)	21–35	Healthy volunteers	1125-night crossover study. AMT 50 mg/day vs. placebo vs. reserpine 0.50 mg/day vs. chlorpromazine 50 mg/day vs. chloral hydrate 500 mg/day vs. chlordiazepoxide 50 mg/day. $N = 14$.	TST increased for AMT relative to placebo throughout trial. SWS increased and SOL decreased early during administration. REMS ("desynchronized sleep") was reduced throughout the trial, most profoundly in the first few days of administration.	Subjects themselves as feeling worse in the morning during AMT treatment. Reports of feeling sick increased for weeks 3 and 4 on and weeks 1 and 2 off medication. Reports of unusual psychologic feelings increased in week 4 on medication.	AMT is probably effective at reducing symptoms of insomnia.
Mendlewicz et al. (1991)	25–68	Depressed inpatients	Retrospective study before treatment with AMT and at 5-7 wk follow up. AMT (165 ± 35 mg/day). $N = 18$.	Marked suppression of REM sleep. Increase in stage 1 and stage 2 NREM sleep and no changes in SWS and latency to sleep onset.	Not assessed.	AMT induces a large REM sleep suppression in depressed inpatients.
Srisurapanont and Jarusuraisin (1998)	18–65	Opiate withdrawal insomnia	6-day randomized, double-blind trial. AMT 25–100 mg/day vs. lorazepam 1–4 mg/day. $N = 27$.	Ease of getting to sleep questionnaire scores on the SEQ were 177.4 ± 53.9 for AMT and 184.5 ± 85.4 for lorazepam, $P = 0.80$. Ease of awakening from sleep on the SEQ was 132.8 ± 47.9 for AMT and 167.6 ± 38.4 for lorazepam, $P = 0.047$.	None of the patients reported any serious AEs during the study. Awakening from sleep after AMT was more difficult than after lorazepam.	AMT is as effective as lorazepam at reducing symptoms of insomnia associated with opiate withdrawal syndrome, though it may be associated with a hangover effect.

5. Other Results. Two studies of amitriptyline as a treatment of secondary insomnia were identified. One study examined amitriptyline's effect on sleep in healthy volunteers when administered chronically (Hartmann and Cravens, 1973) and one study analyzed patients with opiate withdrawal insomnia (Srisurapanont and Jarusuraisin, 1998). The study in healthy volunteers found altered sleep patterns in the group given amitriptyline compared with placebo, with those given the drug displaying increased total sleep time, increased SWS, and less REM ("desynchronized" sleep) (Hartmann and Cravens, 1973). The other study compared amitriptyline 50 mg/day to lorazepam 1–4 mg/day in patients with opiate withdrawal insomnia, finding that although amitriptyline was likely as effective as lorazepam at relieving insomnia symptoms, it may have been associated with a hangover effect the next day (Srisurapanont and Jarusuraisin, 1998).

6. Conclusion. A summary of the effects of amitriptyline on sleep architecture is presented in Table 2. Based on amitriptyline's effect in a study of healthy volunteers (Hartmann and Cravens, 1973) of increasing total sleep time and its efficacy in opiate withdrawal insomnia, there is weak evidence of its efficacy in the treatment of insomnia disorder.

B. Mirtazapine

1. Mechanism of Action. Mirtazapine is classified as a noradrenergic and specific serotonergic antidepressant, because it enhances adrenergic and serotonergic neurotransmission in a manner distinct from other classes of drugs. Its effects as a sedative and as a hypnotic are attributable to its blockade of the histamine H_1 receptor. By antagonizing α_2-autoreceptors it increases norepinephrine release; by antagonizing α_2-heteroreceptors it increases serotonin release, although its effect on serotonergic systems is specific to 5-HT_{1A}-mediated neurotransmission, because it also blocks the 5-HT_2 and 5-HT_3 receptors (Anttila and Leinonen, 2001) (See Table 1 for the list of mirtazapine's main molecular targets). In mice, thermal hyperalgesia and sleep disturbance in a model of neuropathic pain were nearly completely normalized by mirtazapine administration (Enomoto et al., 2012).

2. Indications. Mirtazapine is FDA approved for the treatment of major depressive disorder in adults (US FDA, 2007b). Clinical studies examining the hypnotic effects of mirtazapine are detailed in Table 9.

3. Pharmacokinetics. Mirtazapine is rapidly and completely absorbed and has a half-life of between 20 and 40 hours, with women exhibiting significantly longer elimination half-lives than men (mean half of life 37 hours for women vs. 26 hours for men) (US FDA, 2007b). Peak plasma concentration is reached within 2 hours of administration, and the presence or absence of food does not significantly affect its pharmacokinetics. Plasma levels are linear to dose over a dose range of 15–80 mg. The drug is 85% bound to plasma proteins. The drug's absolute bioavailability is about 50%, and

in vitro data indicate that cytochromes 2D6, 1A2, and 3A are responsible for the formation of its metabolites (US FDA, 2007b).

4. Results in Insomnia Disorder. No studies of mirtazapine as a treatment of primary insomnia were identified, except for a case series (Dolev, 2011) conducted in perimenopausal women who suffered from insomnia ($N = 11$) and who were not depressed by the HAM-D scale (Hamilton, 1960). In this study, the subjects were given mirtazapine 15 mg/day for 2–4 weeks followed by treatment with prolonged-release melatonin 2 mg/day concurrent with the tapering of mirtazapine over 1–3 months. Combination treatment with mirtazapine and melatonin during the tapering period reduced PSQI global scores from 14.45 ± 1 at baseline to 6.00 ± 0.7 at endpoint. Sleep latency as measured by PSQI question 2 decreased from 52.73 ± 14.04 minutes at baseline to 18.64 ± 2.87 minutes at endpoint.

5. Other Results. Five studies of mirtazapine as a treatment of secondary insomnia were identified. There was one open-label study ($N = 36$) in patients with advanced cancer and pain or other distressing symptoms, including insomnia (Theobald et al., 2002); one open-label trial ($N = 6$) in patients diagnosed with major depressive disorder and poor sleep quality (Winokur et al., 2000); one randomized trial ($N = 19$) comparing mirtazapine to fluoxetine in patients diagnosed with major depressive disorder and insomnia (Winokur et al., 2003); one open-label study ($N = 53$) in patients with cancer and comorbid MDD, anxiety disorders, or adjustment disorder (Cankurtaran et al., 2008); and one open-label study ($N = 42$) in patients with cancer and MDD (Kim et al., 2008). In these studies, mirtazapine was generally effective at reducing symptoms of insomnia; in the randomized trial, it was more effective than fluoxetine (Winokur et al., 2003).

6. Conclusion. A summary of the effects of mirtazapine on sleep architecture is presented in Table 2. There is weak evidence that mirtazapine is effective at reducing symptoms of insomnia disorder, based on one case series (Dolev, 2011) and the available open-label evidence of mirtazapine's effectiveness in secondary insomnia.

C. Trazodone

1. Mechanism of Action. Trazodone's effect as a hypnotic is attributable to its moderate antihistaminergic activity at the H_1 receptor, its partial agonism at the $5HT_{1A}$ receptor (Odagaki et al., 2005), its antagonism of the $5HT_{1C}$ and $5HT_2$ receptors, and its antagonism of the postsynaptic α_1-adrenergic receptor (Schatzberg and Nemeroff, 2009; McCall, 2016). It also exerts relatively weak, although specific, reuptake inhibition effects at the 5-HT transporter (see Table 1 for a summary of trazodone's main targets). Thus, trazodone has a mixed profile as both an agonist and an antagonist of serotonin receptors. In rats, trazodone has been shown to increase NREMS without affecting REMS (Lelkes et al., 1994).

2. Indications. Trazodone is FDA approved for the treatment of depression. A survey revealed that trazodone was the first-line choice of 78% or psychiatrists when prescribing medications to treat SSRI-induced insomnia (Dording et al., 2002). As mentioned previously, in 2002, trazodone was the most commonly prescribed medication for insomnia, with 34% more prescriptions than the most commonly prescribed FDA-approved treatment (Walsh, 2004). Clinical studies examining the hypnotic effects of trazodone are detailed in Table 10.

3. Pharmacokinetics. Trazodone's half-life is 7.0 ± 1.2 after multiple oral administration and shows linear pharmacokinetics within the dosage range of 50–150 mg/day (Nilsen et al., 1993). Its absorption is irregular in fasting subjects, but it is improved if the drug is taken after food. However, no differences are observed in the total amount of trazodone absorbed with and without food: its bioavailability values are 65 ± 6% and 63.4%, respectively (Nilsen and Dale, 1992). The drug is primarily metabolized by the liver enzyme CYP3A4, and inhibition of this enzyme by other drugs leads to high blood levels of trazodone (Rotzinger et al., 1998). CYP3A4 mediates the metabolism of trazodone to its main active metabolite, m-chlorophenylpiperazine, which has $5\text{-}HT_{2C}$ agonist and $5\text{-}HT_{2A}$ antagonistic properties (Rotzinger et al., 1998).

4. Results in Insomnia Disorder. One 2-week parallel group RCT ($N = 306$) in patients with primary insomnia was identified (Walsh et al., 1998). The study compared treatment with trazodone 50 mg/day to treatment with zolpidem 10 mg/day and placebo after a 1-week placebo lead-in period. During the first week, both drugs produced significantly shorter self-reported sleep latency and longer self-reported sleep duration than placebo. Sleep latency was significantly shorter with zolpidem than with trazodone. During week 2, only the zolpidem group maintained a significantly shorter sleep latency than the placebo group, and sleep duration did not vary significantly among groups.

5. Other Results. Two reviews on the use of trazodone as a treatment of insomnia were identified (James and Mendelson, 2004; Mendelson, 2005). Both reviews predominantly analyzed studies of trazodone in patients diagnosed with major depressive disorder. Although trazodone was shown to increase total sleep time in patients with MDD (James and Mendelson, 2004), there was limited evidence of its efficacy (Mendelson, 2005). The high rate of discontinuation due to adverse events, which included sedation, dizziness, and psychomotor impairment, make the risk-benefit ratio of trazodone therapy for insomnia uncertain (Mendelson, 2005). Furthermore, there is a risk of priapism in 1 out of 6000 patients treated with trazodone (James and Mendelson, 2004).

TABLE 9
Summary of studies assessing the effects of mirtazapine (MRT) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Aslan et al. (2002)	18–30	Young healthy volunteers	RCT with acute injection of MRT (30 mg) vs. placebo. $N = 20$.	MRT increased stage N3, sleep efficiency, did not alter REM sleep and decreased the number of awakenings and their duration during sleep.	Not analyzed.	MRT is effective in inducing NREM sleep without affecting REM sleep in healthy subjects.
Cankurtaran et al. (2008)	18–65	Cancer with major depressive disorder, anxiety disorders, or adjustment disorder	6-wk open-label trial. MRT 5–30 mg/day vs. imipramine 5–100 mg/day vs. untreated control group that refused drug therapy. $N = 53$.	Percent of patients reporting nightly difficulty falling asleep in MRT group decreased from 65 at baseline to 15 at endpoint vs. a decrease from 53.8 at baseline in imipramine group to 30.8 at endpoint vs. a decrease from 50 at baseline in control group to 30 at endpoint.	Not analyzed.	MRT is effective at reducing symptoms of insomnia in cancer patients, and more effective than imipramine.
Dolev (2011)	45–52	Perimenopausal women with insomnia who did not suffer from depression by HAM-D	Case series. MRT 15 mg/day for 2-4 wk followed by treatment with 2 mg prolonged-release melatonin with tapering of MRT for 1–3 mo. $N = 11$.	Combination treatment with MRT and melatonin during MRT tapering period reduced PSQI global scores from 14.45 ± 1 at baseline to 6.00 ± 0.7 at endpoint. SOL as measured by PSQI question 2 (minute) decreased from 52.73 ± 14.04 at baseline to 18.64 ± 2.87 at endpoint.	No AEs were reported.	MRT followed by prolonged-release melatonin add-on treatment followed by melatonin monotherapy is effective at reducing symptoms of insomnia in perimenopausal women.
Kim et al. (2008)	22–79	Cancer patients with depression	4-wk open-label trial. MRT 15–45 mg/day. $N = 42$.	Amount of sleep (hours) increased from 3.6 ± 1.9 at baseline to 6.8 ± 2.5 at endpoint, $P < 0.001$. Ease of getting to sleep subscale of the Chonnam National University Hospital-Leeds Sleep Evaluation Questionnaire decreased from 4.2 ± 1.0 at baseline to 2.4 ± 1.0 at endpoint, $P < 0.001$.	Four patients discontinued MRT due to side effects (Two due to sedation and one each for general weakness or constipation).	MRT is effective at reducing symptoms of insomnia in cancer patients.
Theobald et al. (2002)	40–83	Advanced cancer patients with pain and other distressing symptoms	Open-label crossover study of MRT 15/30 mg/day. $N = 36$.	There were no significant differences on NRS scales measuring insomnia. However, there was a trend toward improved sleep.	Only one patient withdrew due to MRT side effects.	MRT may be effective at reducing symptoms of insomnia in cancer patients.
Winokur et al. (2000)	18–65	Major depressive disorder with poor sleep quality	2-wk open-label study. MRT 15–30 mg/day. $N = 6$.	SOL improved, $P = 0.009$. TST improved, $P = 0.004$. SE improved, $P = 0.0003$. MRT did not significantly affect REM sleep parameters.	Four of six subjects reported daytime somnolence during week 1, though the complaints resolved by week 2.	MRT is effective at reducing symptoms of insomnia.
Winokur et al. (2003)	18–45	Major depressive disorder with insomnia	8-wk randomized trial. MRT 15–45 mg/day vs. fluoxetine 20–40 mg/day. $N = 19$.	Mean SOL (minute) by polysomnography decreased from 34.3 ± 24.0 at baseline to 10.9 ± 9.6 at Week 9 in MRT group, $P < 0.05$ vs. 38.6 ± 32.2 at baseline to 43.3 ± 28.4 at Week 8 in fluoxetine group. Total sleep time (minute) increased from 327.9 ± 81.8 at baseline to 428.1 ± 73.6 at Week 8 in MRT group, $P < 0.05$ vs. 317.4 ± 68.8 at baseline to 325.1 ± 116.4 in fluoxetine group.	Not analyzed.	MRT is effective at reducing symptoms of insomnia, and superior to fluoxetine.

TABLE 10
Summary of studies assessing the effects of trazodone (TRZ) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Camargos et al. (2014)	60+	Alzheimer's disease	2-wk RCT. TRZ 50 mg/day vs. placebo. $N = 30$.	Actigraphy: TRZ subjects slept 42.5 min more than placebo subjects and percent sleep increased 8.5%. No effect on cognition or WASO or number of awakenings	AEs transient and mild.	Trazodone may be effective at reducing symptoms of insomnia in older adults with Alzheimer's disease.
Cunningham et al. (1994)	18+	Major depression	6-wk RCT of trazodone vs. venlafaxine vs. placebo. 96 responders continued in a 1-yr double-blind continuation phase. Average doses: 156–160 mg/day venlafaxine and 294–300 mg/day TRZ. $N = 225$.	TRZ produced more improvement on the sleep disturbance factor of the HAM-D, but venlafaxine more effective in cognitive disturbance and retardation factors of the HAM-D.	Significantly more patients discontinued TRZ due to dizziness than patients taking placebo or venlafaxine. Significantly more patients discontinued venlafaxine due to nausea.	TRZ is effective at reducing symptoms of insomnia in patients with MDD.
Friedmann et al. (2008)	16–65	DSM-IV current alcohol dependence and sleep disturbance	12-wk RCT. TRZ 50–150 mg/day vs. placebo. $N = 173$.	TRZ group experienced less improvement in proportion of days abstinent during administration of medication, and an increase in the number of drinks per drinking day on cessation of study. TRZ improved sleep quality (PSQI mean change −3.02 [−3.38, −2.67]), but after cessation sleep quality equalized with placebo.	TRZ group reported more dry mouth.	Although TRZ reduced symptoms of insomnia, it may impede improvements in alcoholism during detoxification and lead to increased drinking when stopped.
Haffmans and Vos (1999)	mean: 44	Previous severe major depression; current insomnia secondary to brofaromine treatment	Crossover RCT. TRZ 50 mg/day as adjunct to brofaromine 150–250 mg/day. $N = 7$.	TRZ did not improve SOL, total sleep time, or time awake. TRZ reduced the number of awakenings ($P = 0.019$) and increased stage IV sleep ($P = 0.088$).	While taking TRZ, one patient reported constipation and nausea, one patient reported vertigo, dry mouth, and palpitations, and one patient had tingling feelings in chin and moderate heartburn.	TRZ may not be effective at reducing symptoms of insomnia secondary to treatment with stimulating antidepressants, but may increase slow-wave sleep.
James and Mendelson (2004)	Varied.	Varied.	Review.	TRZ increases total sleep time in patients with MDD, though there are few data to support its use in non-depressed patients.	There is a notable risk of priapism in 1 out of 6000 patients treated with TRZ. There is also a risk of orthostatic hypotension and the induction of cardiac arrhythmias in patients with preexisting cardiac disease.	TRZ has more side effects than conventional hypnotics, making its risk-benefit ratio uncertain.
Karam-Hage and Brower (2003)		*see Gabapentin section*				
Kaynak et al. (2004)	20–50	Insomnia secondary to treatment w/ SSRI, DSM-IV depression	2-wk crossover RCT w/ 1-wk washout. TRZ 100 mg/day + SSRIs vs. placebo + SSRIs. $N = 12$.	TRZ significantly increased total sleep time, percentage of stage 3 and 4 sleep, SE, sleep continuity and decreased number of awakenings. At week 3, completing both TRZ and placebo treatments w/ washout, mean global PSQI scores in both groups reduced from 15 ± 2.5 to 5 ± 1.6. Total polysomnographic sleep time (minute) increased from 382.17 ± 58 to 428 ± 39 on last TRZ night, $P < 0.05$. SOL not significantly improved.	TRZ period associated w/ one subject reporting mild acid indigestion and two reporting mild daytime sedation.	TRZ may be effective at reducing symptoms of SSRI-induced insomnia.

(*continued*)

TABLE 10—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Le Bon et al. (2003)	18–65	Alcohol dependence with physiologic dependence by DSM-IV; alcohol-induced sleep disorders, insomnia type (DSM-IV)	4-wk RCT. TRZ 50 mg/day vs. placebo. $N = 16$.	SE was increased in TRZ group. No benefit in placebo group. HAM-D and CGI were also better in TRZ group.	Most frequent AEs in the TRZ group were hangovers and dizziness. Dose reduction from 200 to 150 mg/day reduced these AEs. In placebo group: AEs included headaches, hangover, and skin irritation.	TRZ may be effective at reducing symptoms of insomnia.
Mendelson (2005)	Varied.	Varied.	Review of 18 studies.	Limited evidence of efficacy of TRZ, many trials were small and were conducted in depressed patients.	High rate of discontinuation due to side effects including sedation, dizziness, and psychomotor impairment. This raises concerns about the use of TRZ in the elderly.	TRZ risk-benefit ratio in insomnia remains uncertain.
Mouret et al. (1988)	35–60	depressed in-patients with a MADRS score >20	Open-label study with TRZ (400–600 mg/day) for 5 wk. $N = 10$.	TRZ decreased latency to sleep onset and intrasleep awakenings, increased TST and did not affect REM sleep time. An increase in REM sleep latency was found only at the end of the 5-wk trial.	Nausea, dizziness.	TRZ is effective at reducing symptoms of insomnia in depressed patients.
Nierenberg et al. (1994)	mean:41.9 S.D.: 10	Antidepressant-associated insomnia in patients treated with fluoxetine or bupropion	Crossover RCT. TRZ 50 mg/day vs. placebo. Mean length of treatment: 6.5 days for TRZ vs. 4.6 days for placebo. $N = 17$.	67% reported improvement with TRZ vs. 13% with placebo. Improvement with TRZ and not placebo on PSQI and Yale-New Haven scores.	Daytime sedation occurred in one patient. Priapism did not occur, but one patient developed a prolonged erection, prompting a dose decrease.	TRZ may be effective at reducing symptoms of insomnia.
Scharf and Sachais (1990)		Depressed patients with sleep disturbances	8-wk single-blind study with TRZ 150–400 mg/day. $N = 6$.	After 5 wk, TRD improved sleep efficiency (from 80.6 ± 12.3% to 91.9 ± 4.9%), increased TST (from 387.1 ± 59.2 to 441.3 ± 23.7 min), prolonged REM sleep latency but did not affect the amount of REM sleep. TRZ enhanced sleep-related penile tumescence.	Not analyzed.	TRZ affects REM sleep in young men and reduced awakenings and movement/arousals probably due to its sedating properties.
Stein et al. (2012)	mean: 38.2 S.D.: 8.6	Methadone maintenance treatment of opioid dependence	6-mo RCT. TRZ 50–150 mg/day vs. placebo. $N = 137$.	Placebo subjects reported significantly higher sleep quality ratings than TRZ subjects, $P = 0.04$. Polysomnography: total sleep time was not significantly improved in TRZ subjects, $P = 0.18$.	Between baseline and 1 mo, TRZ group significantly more likely to report increased thirst or dry mouth, $P = 0.001$, and decreased appetite, $P = 0.04$.	Trazodone is not effective at reducing symptoms of insomnia in patients on methadone maintenance treatment with sleep disturbance.
Walsh et al. (1998)	21–65	Primary insomnia by DSM-IIIR	2-wk parallel-group comparison RCT. TRZ 50 mg/day vs. zolpidem 10 mg/day vs. placebo with 1-wk placebo lead-in. $N = 306$.	During first week, both drugs produced significantly shorter self-reported SOL (SSL) and longer self-reported sleep duration (SSD) than placebo. SSL was significantly shorter with zolpidem than with TRZ. During Week 2, only the zolpidem group maintained a significantly shorter SOL than the placebo group, and SSD did not vary significantly among groups.	Treatment-emergent AEs reported by 65.4% of placebo patients, 76.5% of zolpidem patients, and 75% of TRZ patients. Headache occurred, respectively, in 19%, 24%, and 30% of participants. Somnolence occurred, respectively, in 8%, 16%, and 23% of participants. Treatment generally well-tolerated.	TRZ may be less effective than zolpidem at doses studied at reducing symptoms of insomnia.

(*continued*)

TABLE 10—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Ware et al. (1994)	20–34	Healthy males	Crossover RCT. TRZ 100–200 mg/day vs. nefazodone 200–400 mg/day, vs. buspirone 10–20 mg/day, and vs. placebo. N = 12.	TRZ and buspirone reduced REM sleep amount and increased REM sleep latency whereas nefazodone enhanced REM sleep without affecting REM sleep latency. TRZ The drugs did not affect NREM sleep. TRZ reduced the number of awakenings and the number of movement/arousals compared with placebo	Not analyzed.	TRZ suppress REM sleep and prolongs penile tumescence during sleep.
Yamadera et al. (1998)	21–28	Healthy males	Single-blind study. TRZ 100 mg/day vs. imipramine 40 mg/day vs. placebo. N = 8.	TRZ increased stage N3 and decreased stage N1-N2 vs. placebo, and unlikely imipramine, did not alter REM sleep.	Not analyzed.	TRZ increased NREM sleep without affecting REM sleep in young healthy males.

Nine RCTs on the use of trazodone in the treatment of insomnia secondary to other conditions were identified, of which three were conducted in patients with insomnia secondary to treatment with antidepressants (Nierenberg et al., 1994; Haffmans and Vos, 1999; Kaynak et al., 2004). One crossover RCT (N = 17) of trazodone 50 mg/day versus placebo in antidepressant-associated insomnia secondary to treatment with fluoxetine or bupropion (Nierenberg et al., 1994) and one 2-week crossover RCT (N = 12) of trazodone 100 mg/day versus placebo in patients with insomnia secondary to treatment with SSRIs (Kaynak et al., 2004) found trazodone effective, with significantly increased total sleep time, sleep efficiency, sleep continuity, and increased stage 3 and stage 4 sleep in the second trial. However, one smaller RCT (N = 7) of trazodone 50 mg/day in antidepressant-associated insomnia secondary to treatment with brofaromine (Haffmans and Vos, 1999) found that trazodone did not improve sleep latency, total sleep time, or time awake versus placebo, although it increased SWS. These results suggest that trazodone may be effective in cases of insomnia induced by SSRIs or bupropion, but not brofaromine, an antidepressant that was never brought to market.

A 6-week study of trazodone versus venlafaxine versus placebo in patients diagnosed with major depression was also identified (Cunningham et al., 1994): in this study, trazodone was more effective for improving sleep disturbance on the HAM-D, but venlafaxine was better at relieving cognitive disturbance and retardation. Trazodone caused more dizziness while venlafaxine caused more nausea.

Three studies of trazodone in the context of addiction were identified. One 4-week RCT (N = 16) of trazodone 50 mg/day versus placebo in patients with alcohol-induced insomnia and alcohol dependence (Le Bon et al., 2003) found that trazodone increased sleep efficiency. However, caution is warranted because a large 12-week RCT (N = 173) of trazodone 50–150 mg/day versus placebo in patients with alcohol dependence and sleep disturbances (Friedmann et al., 2008) found though trazodone reduced symptoms of insomnia, and the trazodone group experienced less improvement in the proportion of days abstinent during detoxification when receiving medication; furthermore, the trazodone group had an increase in the number of drinks per drinking day upon cessation of the study. A 6-month RCT (N = 137) of trazodone 50–150 mg/day during methadone maintenance treatment of opioid dependence (Stein et al., 2012) was negative, with placebo-treated subjects reporting significantly higher sleep quality ratings than trazodone-treated subjects.

Finally, a 2-week RCT (N = 30) of trazodone 50 mg/day in patients with Alzheimer's disease found that trazodone-treated subjects slept significantly longer than placebo-treated subjects, although the drug did not have a detectable effect on cognition (Camargos et al., 2014).

6. Conclusion. A summary of the effects of trazodone on sleep architecture is presented in Table 2. There is good evidence that trazodone is effective at reducing symptoms of insomnia in patients with SSRI-induced insomnia based on two RCTs (Nierenberg et al., 1994; Kaynak et al., 2004). Trazodone use is discouraged in insomnia associated with opioid dependence or alcoholism based on one negative RCT in patients on methadone maintenance treatment (Stein et al., 2012) and the safety concerns in one RCT conducted in patients with alcoholism (Friedmann et al., 2008).

D. Low-Dose Doxepin (<6 mg/day)

1. Mechanism of Action. Doxepin is a tricyclic antidepressant with significant antihistaminic effects. Doxepin is the most potent antihistamine of the tricyclic antidepressants, with four times the potency of amitriptyline and 800 times the potency of diphenhydramine at the H_1 receptor (Richelson, 1979; Gillman, 2007). At standard antidepressant doses, >75 mg/day, doxepin inhibits the reuptake of serotonin and norepinephrine and antagonizes cholinergic, histaminergic, and α-adrenergic activity. As a hypnotic, doxepin is used at low doses; at doses <10 mg/day, it theoretically affects only the histamine receptor, with no meaningful effects on the noradrenergic and serotonergic systems (McCall, 2016) (see Table 1).

2. Indications. Low-dose doxepin , under the brand name Silenor (Pernix Therapeutics, Morristown, NJ), is FDA approved for the treatment of insomnia characterized by difficulties with sleep maintenance to a maximum dose of 6 mg/day (US FDA, 2010b). Doxepin is also approved as an antidepressant in the treatment of "psychoneurotic patients with depression and/or anxiety." Clinical studies examining the hypnotic effects of low-dose doxepin are detailed in Table 11.

3. Pharmacokinetics. Low-dose doxepin has a terminal half-life of 15.3 hours, whereas the half-life of nordoxepin, Median to peak concentration (T_{max}) of doxepin 6 mg occurs 3.5 hours after oral administration to healthy fasted subjects; T_{max} is delayed by approximately 3 hours if the drug is taken with a high-fat meal, whereas AUC is increased by 41% and C_{max} by 15% (US FDA, 2010b). For this reason, it is recommended that doxepin be taken without food, to minimize the risk of next day effects. The major liver enzymes responsible for the metabolism of doxepin are CYP2C19 and CYP2D6, whereas CYP1A2 and CYP2C9 are involved to a lesser extent. The drug is 80% bound to plasma proteins. Notably, doxepin interacts with cimetidine (causes a twofold increase in doxepin C_{max} and AUC) and sertraline (causes AUC to be increased 21% and C_{max} to be increased 32%) (US FDA, 2010b).

4. Results in Insomnia Disorder. One systematic review (Yeung et al., 2015), five published RCTs (Roth et al., 2007; Scharf et al., 2008a; Krystal et al., 2011, 2010; Lankford et al., 2012), and one unpublished RCT (Takeda Global Research & Development Center Inc., 2008) of low-dose doxepin as a treatment of primary insomnia were identified. The systematic review included two studies of doxepin at antidepressant doses (25–300 mg/day) that are excluded in this review. The authors did not perform meta-analysis of pooled results due to heterogeneity but confirmed that low-dose doxepin had a small to medium effect size versus placebo for sleep maintenance and sleep duration, but was ineffective at improving the time to sleep onset. The findings in the individual RCTs cited above generally came to similar conclusions as the recent systematic review, although some RCTs used subjective measurements and others used polysomnographic measurements.

The unpublished clinical trial is a double-dummy study of ramelteon + low-dose doxepin versus each drug as monotherapy versus placebo (Takeda Global Research & Development Center Inc., 2008). It found that ramelteon + low-dose doxepin was significantly more effective than ramelteon + placebo by polysomnography-measured wake time after sleep onset and total sleep time, as well as subjective wake time after sleep onset.

5. Other Results. A single night RCT of low-dose doxepin in healthy volunteers was also identified (Roth et al., 2010). In this trial, the investigators attempted to induce transient insomnia using the first-night effect as well as a 3-hour phase advance. Low-dose doxepin was effective at reducing latency to sleep and increasing total sleep time.

6. Conclusion. A summary of the effects of low-dose doxepin on sleep architecture is presented in Table 2. There is strong evidence that low-dose doxepin is effective at reducing symptoms of primary insomnia based on one systematic review (Yeung et al., 2015), five published RCTs (Roth et al., 2007; Scharf et al., 2008a; Krystal et al., 2011, 2010; Lankford et al., 2012), and one unpublished RCT (Takeda Global Research & Development Center Inc., 2008). Low-dose doxepin exerts a strong on improving sleep maintenance.

VII. Anticonvulsant Drugs

A. Gabapentin

1. Mechanism of Action. Gabapentin is an anticonvulsant drug that binds to the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels (Gee et al., 1996) (Table 1). It crosses several lipid membrane barriers; in vitro, it has been shown to modulate the activity of the GABA synthesizing enzyme, glutamic acid decarboxylase, and the glutamate synthesizing enzyme, branched-chain amino acid transaminase (Taylor, 1997). Its modulation of the GABAergic and glutamatergic systems probably underlies its effect as a hypnotic and anxiolytic. Gabapentin is known to increase SWS without affecting other polygraphic variables and without causing increased drowsiness during the day

TABLE 11
Summary of studies assessing the effects of low-dose doxepine (DXP) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Krystal et al. (2010)	65+	Primary insomnia by DSM-IV	12-wk RCT. DXP 1 mg/day vs. 3 mg/day vs. placebo. N = 240.	LPS was not significantly different from placebo for any dose of DXP. However, WASO was significantly reduced at all time points in the DXP 3 mg/day group ($P < 0.001$) and on night 1 ($P < 0.01$) and night 85 ($P < 0.05$), but not night 29 in the DXP 1 mg/day group. TST was increased significantly in the DXP 3 mg/day group at all time points and in the DXP 1 mg/day group at night 1 ($P < 0.05$) and night 85 ($P < 0.05$) but not night 29.	Rates of treatment-emergent AEs were lower in the DXP groups than the placebo group: 52% of placebo subjects reported an AE compared with DXP 1 mg/day (40%) and DXP 3 mg/day (38%). Less discontinuation with DXP as well: placebo discontinuation was 14%, DXP 1 mg/day was 9%, DXP 3 mg/day was 10%. No evidence of next-day sedation.	Low-dose DXP is effective at reducing symptoms of insomnia.
Krystal et al. (2011)	18–64	Primary insomnia by DSM-IV-TR	35-day RCT followed by two nights of single-blind placebo treatment to assess discontinuation effects. DXP 3 mg/day vs. 6 mg/day vs. placebo. N = 221.	By polysomnography: LPS was only improved relative to placebo in both DXP 3 and 6 mg/day on night 1, $P < 0.0001$, and not improved on night 15 or 29. TST was significantly improved for both doses and for all time points except night 15 in the 3 mg/day group. WASO was significantly improved at all time points and in both dosage groups.	Rates of discontinuation were similar between treatment arms: placebo = 12%, DXP 3 mg/day = 12%, DXP 6 mg/day = 11%. No clinically meaningful changes in mean laboratory values, ECGs, body weight, or vital signs.	Low-dose DXP is effective at reducing symptoms of insomnia. DXP seems particularly effective at maintaining sleep.
Lankford et al. (2012)	65+	Primary insomnia by DSM-IV-TR	4-wk RCT. DXP 6 mg/day vs. placebo. N = 255.	Subjective TST (minute) increased from 283.1 ± 50.0 to 346.1 ± 66.4 at week 4 in the DXP group vs. an increase from 293.5 ± 49.1 to 336.4 ± 64.7 at week 4 in the placebo group, $P < 0.01$ (DXP separated from placebo on this measure by week 1). Subjective WASO was reduced relative to placebo at week 1 ($P < 0.0001$) and week 4 ($P < 0.01$).	Rates of AEs were similar between groups: 27% for placebo and 31% for DXP 6 mg/day. Rates of discontinuation were lower for DXP: placebo = 10% vs. DXP 6 mg/day = 5%. No changes in laboratory values, ECGs, body weight, neurologic examinations, or vital signs.	Low-dose DXP is effective at reducing symptoms of insomnia.
NCT#00755495	*see Ramelteon section*					
Roth et al. (2007)	18–64	Chronic primary insomnia by DSM-IV	Four-group crossover RCT with 2 polysomnographic assessment nights per treatment. DXP 1 mg/day vs. 3 mg/day vs. 6 mg/day vs. placebo. N = 67.	For the measurement of LPS (polysomnography), none of the treatments were statistically better than placebo by one analysis; a statistical re-analysis post hoc found P = 0.0139 for DXP 6 mg. All three doses improved total sleep time relative to placebo: P = 0.0005 for DXP 1 mg/day, $P < 0.0001$ for DXP 3 mg/day, $P < 0.0001$ for DXP 6 mg/day.	AEs in the DXP groups occurred at a similar rate of those in the placebo group and did not appear to be dose-related. Headache and somnolence were the most common AEs.	Low-dose DXP is effective in the treatment of insomnia. All doses of DXP significantly improved SE during the entire night, each one $P < 0.05$. Only DXP 3 mg/day and DXP 6 mg/day significantly improved wake time during sleep.
Roth et al. (2010)	25–55	Healthy participants required to have no history of insomnia and normal sleep patterns during last 3 mo. Transient insomnia was induced in participants.	One night RCT. DXP 6 mg/day vs. placebo. N = 565.	By polysomnography: LPS was 47.7 ± 59.5 min in the placebo group and 31.8 ± 44.0 min in the DXP group, $P < 0.0001$. TST was increased 51.1 min in the DXP group relative to the placebo group, $P < 0.0001$.	Incidence of AEs was similar to placebo. On one measure of next-day residual effects (the Digit Symbol Substitution Test) there was no difference between DXP and placebo. However, DXP resulted in statistically significant worsening on two other scales, the Symbol Copying Test and the Visual Analog Scale for sleepiness.	DXP is effective at reducing symptoms of insomnia.

(*continued*)

TABLE 11—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Scharf et al. (2008b)	65+	Primary insomnia by DSM-IV	Four-period crossover RCT. DXP 1 vs. 3 vs. 6 mg/day vs. placebo. $N = 76$.	LPS was not significantly different from placebo for any dose of DXP. However, TST and SE were significantly increased relative to placebo for all doses, $P < 0.0001$. Wake time during sleep were significantly reduced at all doses, $P < 0.0001$.	Number of AEs was similar between placebo and DXP and were similar between DXP doses.	Low-dose DXP is effective at reducing symptoms of insomnia. It also increases SE. DXP seems particularly effective at maintaining sleep.
Yeung et al. (2015)	>18	Varied	Systematic review and meta-analysis of nine placebo-controlled RCTs.	Pooled results were largely not reported due to heterogeneity; however, the authors were able to conclude the significant efficacy and safety of DXP 3–6 mg for one to two nights.	In young and middle-aged adults, the incidence of any AEs were 27%, 35%, and 32% in placebo, DXP 3 mg/day (RR = 1.27, 95% CI = 0.8, 2.1, $P = 0.29$), and DXP 6 mg/day (RR = 1.30, 95% CI 0.8, 2.1, $P = 0.29$). Common AEs were headache, somnolence, and nausea. Results in older adults were similar.	Low-dose DXP is effective at reducing symptoms of insomnia.

(Foldvary-Schaefer et al., 2002). In mice, gabapentin alleviates sleep disturbances induced by a neuropathic pain-like condition (Takemura et al., 2011).

2. Indications. Gabapentin is FDA-approved for the management of postherpetic neuralgia in adults (US FDA, 2014c). It is FDA approved as adjunctive treatment of partial seizures with and without secondary generalization in patients over 12 years old with epilepsy and as adjunctive treatment of partial seizures in patients aged 3–12. Clinical studies examining the hypnotic effects of gabapentin are detailed in Table 12.

3. Pharmacokinetics. The bioavailability of gabapentin is inversely proportional to its daily dose: as dosage increases, bioavailability decreases. The bioavailability of gabapentin is 60%, 47%, 34%, 33%, and 27% following oral administration of 900, 1200, 2400, 3600, and 4800 mg/day of the drug given in three divided doses (US FDA, 2014c). Less than 3% of gabapentin is bound to plasma protein, and the drug is not appreciably metabolized in humans. Its elimination half-life is 5–7 hours and is unaltered by dose or following multiple dosing. Taking the drug with food has a small effect on its pharmacokinetics, increasing AUC and C_{max} by 14% each.

4. Results in Insomnia Disorder. One open-label trial conducted in patients with primary insomnia was identified (Lo et al., 2010). This study ($N = 18$; mean dose of gabapentin 540 mg/day, range 200–900 mg/day) found polysomnographic evidence of increased sleep efficiency (80.00%–87.17%, $P < 0.05$) and SWS (10.47%–17.68%, $P < 0.005$) and decreased wake time after sleep onset (16.45%–7.84%, $P < 0.05$) (Lo et al., 2010). However, gabapentin did not significantly improve sleep onset latency (17.58–14.58 minutes, not significant).

5. Other Results. Five other studies of gabapentin were identified. Two of the four studies were RCTs: one was conducted in patients diagnosed with alcohol dependence and comorbid insomnia (Brower et al., 2008) and the other was a single-dose study conducted in patients with "occasional disturbed sleep" (Rosenberg et al., 2014). One open-label comparison study of gabapentin versus trazodone conducted in patients with alcohol dependence and "persistent insomnia" (Karam-Hage and Brower, 2003) and an open-label study conducted in children suffering from refractory insomnia comorbid to neurodevelopmental or neuropsychiatric disorders (Robinson and Malow, 2013) were also identified. Finally, one study in healthy subjects was identified (Foldvary-Schaefer et al., 2002).

In the RCT conducted in patients with alcohol dependence and comorbid insomnia ($N = 21$; gabapentin 1500 mg/day), treatment group did not predict changes in the Sleep Problems Questionnaire score (Brower et al., 2008). However, gabapentin treatment significantly reduced the risk of relapse to heavy drinking: at

TABLE 12
Summary of studies assessing the effects of gabapentin (GBP) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Brower et al. (2008)	18+	Alcohol dependence with comorbid insomnia	6-wk RCT plus 2-wk placebo lead-in and follow up visit after 6 wk. GBP 1500 mg/day vs. placebo. $N = 21$.	60% of GBP group relapsed to heavy drinking by 12 wk vs. 100% of the placebo group, $P = 0.04$. Treatment group did not predict changes in Sleep Problems Questionnaire (SPQ) score. There were no significant polysomnographic differences between groups.	The most common side effects attributed to gabapentin vs. placebo, respectively, were somnolence (three subjects vs. one subject), headache (three subjects in each group), dizziness (two subjects vs. one subject), indigestion (two vs. four subjects), nerve or muscle pain (two subjects vs. none) .	GBP is not effective at reducing symptoms of insomnia, though it delayed the onset to heavy drinking.
Foldvary-Schaefer et al. (2002)	20–46	Healthy participants	Randomized study. GBP titrated to 1800 mg/day vs. untreated group. $N = 19$.	GBP-treated subjects had an increase in SWS compared with baseline. No difference in other polygraphic variables. GBP subjects had minor reductions in arousals, awakenings, and stage shifts was observed in treated subjects.	One patient experienced dizziness at highest dose and was treated with 1500 mg/day.	GBP may be effective at increasing SWS without affecting other aspects of sleep.
Karam-Hage and Brower (2003)	mean: 44 S.D.: 14	DSM-IV alcohol dependence with persistent insomnia	4–6-wk open-label study. GBP 300–1800 mg/day vs. trazodone 25–300 mg/day. $N = 55$.	Both groups showed significant improvement in sleep from baseline to follow up, $P < 0.001$ for each group as measured by the SPQ. Total change in SPQ scores between the groups: GBP group improved by 8.8 ± 4.0 while trazadone group improved 6.1 ± 3.4, $P = 0.023$.	Both medications were well-tolerated.	GBP is effective at reducing symptoms of insomnia in alcoholism and significantly more effective than trazodone.
Lo et al. (2010)	mean: 43.2 S.D.: 15.4	Primary insomnia	4-wk open-label study. GBP 200–900 mg/day. $N = 18$.	By polysomnography: GBP did not significantly improve SOL, which decreased from 17.58 to 14.58 min. GBP improved SE from 80.00% to 87.17%, $P < 0.05$. WASO was significantly reduced from 16.45% to 7.84%, $P < 0.05$. Sleep stage N3 increased from 10.47% to 17.68%, $P < 0.005$.	Prolactin levels were significantly reduced after GBP treatment; whether the effect occurred as a result of GBP was uncertain.	GBP is effective at reducing symptoms of insomnia and increases slow-wave sleep.
Robinson and Malow (2013)	Pediatric: mean 7.2	Refractory insomnia in children with neurodevelopmental or neuropsychiatric disorders	Open-label study. GBP 6–15 mg/kg per day. $N = 23$.	Improved sleep was noted in 78% of children.	AEs noted in six children, mostly agitation and worsened ability to sleep.	GBP is effective at reducing symptoms of insomnia in children with neurodevelopmental and neuropsychiatric disorders.
Rosenberg et al. (2014)	18 and older	Occasional disturbed sleep	RCT using a 5-h phase advance insomnia model. GBP 250 mg vs. GBP 500 mg vs. placebo. $N = 377$.	LPS was not significantly different among groups. Mean total sleep time was significantly greater for the gabapentin groups: 311.4 ± 8.4 min in placebo group, 356.5 ± 7.5 min in GBP 250 mg, and 378.8 min in GBP 500 mg group. Percent slow-wave sleep was significantly greater in GBP groups, 12.6%, 15.4%, and 17.0%, respectively.	4.2% of participants reported at least one AE, with 1.6% of placebo participants, 4.0% of GBP 250 mg/day participants, and 7.2% GBP 500 mg/day. The most common AE was headache.	GBP is effective at reducing symptoms of insomnia and increases slow-wave sleep.

12 weeks, 60% of the gabapentin group had relapsed compared with 100% of the placebo group. Similarly, in the single-dose study using a 5-hour phase advance model in patients with "occasional disturbed sleep," gabapentin 250 mg/day and gabapentin 500 mg/day were not significantly superior to placebo at reducing latency to persistent sleep. However, the mean total sleep time was significantly greater for the gabapentin groups: 311.4 [8.4] min in the placebo group versus 356.5 [7.5] min in the gabapentin 250 mg/day group ($P \leq 0.001$ compared with placebo) and 378.7 [7.3] min in the gabapentin 500 mg/day group ($P \leq 0.001$ compared with placebo, $P \leq 0.01$ compared with gabapentin 250 mg/day). Wake after sleep onset was significantly improved in the gabapentin groups, as was the proportion of time spent in SWS (stages 3 and 4) (Rosenberg et al., 2014). Finally, in the open-label comparison study of gabapentin and trazodone in alcoholism, gabapentin was significantly more effective.

6. Conclusion. A summary of the effects of gabapentin on sleep architecture is presented in Table 2. There is some evidence that gabapentin is effective in the treatment of insomnia disorder according to one open-label trial, although it did not significantly improve sleep onset latency (Lo et al., 2010).

B. Pregabalin

1. Mechanism of Action. Similar to gabapentin, pregabalin binds to $\alpha_2\delta$ subunit-containing voltage-gated calcium channels (Taylor et al., 2007). Pregabalin also modulates the influx of calcium at nerve terminals, which may accounts for its therapeutic benefit in neuropathic pain, seizures, and anxiety. The mechanism of action of pregabalin (Table 1) in improving sleep has not been completely elucidated, but it is known to be different from benzodiazepines as pregabalin is not active at GABA-A or benzodiazepine receptors (Taylor et al., 2007). Furthermore, although benzodiazepines typically reduce SWS, pregabalin has been found to increase it (Hindmarch et al., 2005). In rats, pregabalin has been found to increase NREMS and REMS, while markedly increasing the duration of NREMS episodes and reducing their number (Kubota et al., 2001). In one study, pregabalin increased NREMS in mice with a neuropathic pain-like condition, but not normal mice (Wang et al., 2015).

2. Indications. Pregabalin is FDA approved for the management of neuropathic pain associated with diabetic peripheral neuropathy, the management of postherpetic neuralgia, adjunctive therapy for adult patients with partial onset seizures, the management of fibromyalgia, and the management of neuropathic pain associated with spinal cord injury (US FDA, 2016). Clinical studies examining the hypnotic effects of gabapentin are detailed in Table 13.

3. Pharmacokinetics. Following oral administration, peak plasma concentrations of pregabalin occur within 1.5 hours; its bioavailability is greater than or equal to 90% and is independent of dose (US FDA, 2016). The half-life of pregabalin is about 6 hours. Taking pregabalin with food increases T_{max} to approximately 3 hours and reduces C_{max} by 25%–30%, although pregabalin can be taken with or without food. It does not bind to plasma proteins and undergoes negligible metabolism in humans (US FDA, 2016). Oral clearance tends to decrease with increasing age.

4. Results in Insomnia Disorder. No studies of pregabalin as a treatment of insomnia disorder were identified.

5. Other Results. Three reviews were found analyzing the use of pregabalin in patients with insomnia: in two, patients were primarily diagnosed with generalized anxiety disorder (Montgomery et al., 2009; Holsboer-Trachsler and Prieto, 2013), and in one, patients were primarily diagnosed with fibromyalgia (Russell et al., 2009). In the most recent review, pooled data from four RCTs ($N = 1354$) established that among patients with severe difficulty in falling asleep, remission was observed in 54.0% of the pregabalin group versus 29.8% of placebo group (Holsboer-Trachsler and Prieto, 2013). In those with severe difficulty in staying asleep, remission was observed in 54.2% of pregabalin group versus 26.7% of placebo group. Finally, in those with severe difficulty associated with waking up too early, remission was observed in 59.4% of pregabalin group versus 34.6% of placebo group. The fibromyalgia study ($N = 1493$, two RCTs) likewise found that pregabalin was significantly superior to placebo in reducing the burden of insomnia symptoms as measured using the Sleep Quality Diary and Medical Outcomes Study Subscales of Sleep Disturbance, Quantity of Sleep, and Sleep Problems Index (Russell et al., 2009). For more information about these psychometric scales, see Smith and Wegener (2003).

6. Conclusion. A summary of the effects of pregabalin on sleep architecture is presented in Table 2. There is good evidence based on two reviews (Montgomery et al., 2009; Holsboer-Trachsler and Prieto, 2013) that pregabalin is effective at reducing symptoms of insomnia in generalized anxiety disorder. There is also good evidence based on one review (Russell et al., 2009) that pregabalin is effective at reducing symptoms of insomnia in fibromyalgia. Based on these same reviews, there is weak evidence that pregabalin is effective in the treatment of insomnia disorder.

VIII. Atypical Antipsychotic Drugs

Sedating atypical antipsychotics, particularly quetiapine, are often used in the clinic for the management of insomnia disorder and insomnia symptoms that occur comorbid to psychiatric illness (Pringsheim and Gardner, 2014). Although they are effective in the management of bipolar and psychotic disorders, systematic

TABLE 13
Summary of studies assessing the effects of pregabalin (PGB) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
De Haas et al. (2007)	19–67	Epilepsy and subjective sleep disturbances	4-wk RCT parallel-group study. PGB 300 mg/day twice a day vs. placebo twice a day. $N = 17$.	PGB had positive effect on disturbed sleep based on subjective assessments (questionnaires) but not on polysomnographic measures. PSG reduced only the number of awakenings ($P = 0.04$ vs. placebo).	Mild to moderate. Headache was the most frequent AE. Other AEs were dizziness and somnolence.	PGB improves sleep continuity and subjective sleep quality in epileptic patients with sleep complaints.
Hindmarch et al. (2005)	18–50	Healthy adult volunteers	Randomized, double-blind, placebo- and active-controlled, three-way crossover. PGB 150 mg three times a day vs. alprazolam 1 mg three times a day vs. placebo three times a day for 3 days. $N = 24$.	PGB increased TST, stage N3, and sleep efficiency, and decreased SOL and REM sleep.	NS	PGB has significant effects on the sleep of healthy humans that are different from those of BZD; particularly, it increases SWS and sleep continuity.
Holsboer-Trachsler et al. (2013)	NS	Generalized anxiety disorder	Review of seven RCTs. PGB 150–600 mg/day vs. placebo.	Pooled remission data in insomnia symptoms from four 4–6 wk RCTs ($N = 1354$): "Severe" difficulty of falling asleep, remission observed in 54.0% of PGB group vs. 29.8% of placebo group; "severe" difficulty in staying asleep, remission observed in 54.2% of PGB group vs. 26.7% of placebo group; "severe" difficulty with waking up too early, remission observed in 59.4% of PGB group vs. 34.6% of placebo group.	Most frequent adverse effects, like somnolence and dizziness, are most common in first 2 wk of therapy. The incidence of somnolence as an AE in patients with moderate to severe insomnia was lower than for benzodiazepines: PGB 150 mg/day: 24.4%, PGB 300-450 mg/day: 26.2%, PGB 600 mg/day: 31.5%, alprazolam/lorazepam: 54.2%, placebo: 7.8%.	PGB is effective at reducing symptoms of insomnia in generalized anxiety disorder.
Montgomery et al. (2009)		Generalized anxiety disorder	Review of six RCTs. $N = 1854$.	In patients presenting with high insomnia, PGB produced significantly greater improvement on HAM-A total scores: PGB 300–450 mg/day (-13.1 ± 0.6); PGB 600 mg/day (-11.2 ± 0.5) dose groups compared with placebo (-8.3 ± 0.5; $P < 0.0001$ for both comparisons). PGB 150 mg/day was not significant (-9.9 ± 0.7; $P = 0.051$).	Total discontinuations were lower than placebo (25.9%) for pregabalin 150 mg/day (16.4%) and 300–450 mg/day (16.4%), nonsignificantly higher for pregabalin 600 mg (27.6%), and significantly higher for alprazolam/lorazepam (38.0%, respectively; $P < 0.05$.	PGB 300–600 mg/day is effective at reducing symptoms of anxiety in patients presenting with generalized anxiety disorder with high levels of insomnia.
Russell et al. (2009)	18+	Fibromyalgia	Review of two RCTs. PGB 300, 450, or 600 mg/day vs. placebo. $N = 1493$.	Both studies found significant improvement in PGB group relative to placebo group on: Sleep Quality Diary and MOS Subscales of Sleep Disturbance, Quantity of Sleep, and Sleep Problems Index. Pooled results not listed.	Not analyzed.	PGB is effective at reducing symptoms of insomnia in fibromyalgia.

reviews have found a lack of evidence for the use of sedating atypical antipsychotics and explicitly recommend against prescribing them for insomnia disorder (Thompson et al., 2016). The 2016 meta-analysis acknowledges that the use of atypical antipsychotics may be appropriate in patients who have failed other treatment modalities and who have a comorbid condition that could benefit from the primary action of the drug (based on consensus of experts in sleep medicine). Similarly, guidelines for the treatment of chronic insomnia report insufficient evidence for atypical antipsychotics as first-line therapy (Schutte-Rodin et al., 2008), but state that the medications may be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect.

A. Olanzapine

1. Mechanism of Action. Olanzapine is an atypical antipsychotic with affinity for the dopamine D_1, D_2, and D_4 receptors; the serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors; the α_1-adrenergic receptor; the histamine H_1 receptor; and five muscarinic receptor subtypes (Bymaster et al., 1996). Its hypnotic effects are probably attributable to its strong antagonism of the H_1 antagonism as well as its antagonism of serotonin receptors. In an assay of compounds tested at the histamine H_1 receptor, olanzapine was the most potent compound Richelsen and Souder (2000) had tested of any class of compounds. Olanzapine seems to specifically increase SWS (Salin-Pascual et al., 1999; Giménez et al., 2007; Kluge et al., 2014). Main molecular targets of olanzapine are summarized in Table 1.

2. Indications. Olanzapine is FDA approved for the treatment of schizophrenia in adults and adolescents; for the acute treatment of manic or mixed episodes associated with bipolar I disorder and the maintenance treatment of bipolar I disorder in adults and adolescents; and, as an intramuscular injection, for the treatment of acute agitation associated with schizophrenia and bipolar I mania (US FDA, 2009). Clinical studies examining the hypnotic effects of olanzapine are detailed in Table 14.

3. Pharmacokinetics. Olanzapine reaches peak concentrations about 6 hours following oral administration, and its elimination half-life ranges from 21 to 54 hours, with a mean of 30 hours (US FDA, 2009). It is eliminated extensively by first-pass metabolism: about 40% of an oral dose is metabolized before it reaches the systemic circulation. Olanzapine is extensively metabolized by CYP1A2, CYP2D6, and the flavin monooxygenase system, although its metabolites do not display pharmacological activity at normal concentrations (US FDA, 2009). Its pharmacokinetics are not affected by food. The drug is 93% bound to plasma protein. Clearance of olanzapine is approximately 30% lower in women than in men, and the elimination half-life of olanzapine is about 1.5 times higher in subjects greater than 65 years old.

4. Results in Insomnia Disorder. No studies of olanzapine as a treatment of insomnia disorder were identified.

5. Other Results. Two studies that examined olanzapine's effect on sleep (Salin-Pascual et al., 1999; Sharpley et al., 2000) and three studies on olanzapine as a treatment of secondary insomnia were identified (Jakovljević et al., 2003; Khazaie et al., 2010, 2013). Of the studies analyzing olanzapine's effect on sleep, both were small: one was an open-label study conducted in 20 patients with schizophrenia, during which polysomnographic recordings were taken for 5 days, with patients only receiving olanzapine on two nights (Salin-Pascual et al., 1999) and one was a one-dose crossover RCT conducted in nine healthy male participants, with 7–14 days washout between doses (Sharpley et al., 2000). The crossover RCT examined olanzapine 5, 10 mg/day or placebo, whereas the study in patients with schizophrenia examined olanzapine 10 mg/day. Both studies found that olanzapine profoundly increased slow-wave sleep and increased total sleep time as acute treatment.

Of the studies in secondary insomnia, one was conducted in patients suffering from treatment-resistant posttraumatic stress disorder (PTSD) (Jakovljević et al., 2003), whereas the other two were in patients with paradoxical insomnia, also known as sleep state misperception (Khazaie et al., 2010, 2013). The first study was in patients suffering from intractable PTSD in which open-label olanzapine was added to their current medications (Jakovljević et al., 2003). The patients had recurrent nightmares and insomnia resistant to numerous medications. In all five cases, olanzapine resulted in a significant improvement in their symptoms. One randomized, open-label study was conducted in patients diagnosed with paradoxical insomnia, or sleep-state misperception (Khazaie et al., 2013). Patients suffering from this disorder complain of difficulties with initiating and maintaining sleep; however, the hallmark of paradoxical insomnia is that objective polysomnographic measures find that the patients are getting sufficient sleep. In this study, the investigators followed up on a case report study they had published in 2010 - (Khazaie et al., 2010), in which they reported successful treatment of recalcitrant, paradoxical insomnia with olanzapine in a single patient. The group's larger study compared treatment with two different atypical antipsychotics: olanzapine and risperidone. They found that, although both treatments were associated with significant improvements in subjective sleep quality, olanzapine was significantly superior to risperidone, as measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989).

6. Conclusion. A summary of the effects of olanzapine on sleep architecture is presented in Table 2. There is weak evidence that olanzapine acutely increases slow-wave sleep and total sleep time (Salin-Pascual

TABLE 14
Summary of studies assessing the effects of olanzapine (OLA) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Jakovljević et al. (2003)	28–50	Treatment-resistant PTSD with nightmares and insomnia	Case series. OLA added to current treatment regimen. $N = 5$.	All five patients improved rapidly after treatment initiation with olanzapine.	No AEs were reported.	OLA may be effective at reducing sleep disturbances in PTSD.
Khazaie et al. (2013)	60	Paradoxical insomnia	Case report. OLA 5 mg/day added to treatment regimen. $N = 1$.	After 6 wk, OLA treatment resulted in complete remission of symptoms.	None listed.	OLA may be effective at reducing symptoms of paradoxical insomnia.
Khazaie et al. (2013)	Mean: 53.4; S.D.: 14.4	Paradoxical insomnia	8-wk randomized, open-label trial. OLA 10 mg/day vs. risperidone 4 mg/day. $N = 29$.	Sleep quality measured with the Pittsburgh Sleep Quality Inventory showed significant improvement in both treatment groups, though improvement in OLA group was superior to risperidone group. In OLA group, baseline mean was 11.8 $\pm$ 2.3 and treatment mean was 2.6 $\pm$ 1.6, $P < 0.001$. In risperidone group, baseline mean was 11.1 $\pm$ 2.4 and treatment mean was 5 $\pm$ 3.8, $P < 0.001$. Between groups comparison yielded $P < 0.04$.	No AEs were reported.	OLA is effective at reducing symptoms of paradoxical insomnia.
Kluge et al. (2014)	18–65	Schizophrenia and review of the literature	6-wk RCT single center. OLA 5-25 mg/day vs. clozapine 100–400 mg/day. During the first 2 wk, the dose range was restricted (OLA 10–15 mg/day, clozapine 25–200 mg/day). $N = 30$.	OLA and clozapine increased TST and sleep efficiency, and decreased SOL. Concerning sleep stages, OLA increased SWS and decreased REM sleep.	No clinically relevant symptoms of restless legs syndrome were observed. No other AEs were analyzed.	OLA is effective in improving sleep in patients with schizophrenia.
Salin-Pasqual et al. (1999)	Mean: 33.6; S.D.: 10.7	Schizophrenia	Five-night open-label polysomnographic study with OLA 10 mg/day administered for two nights. $N = 20$.	OLA enhanced slow wave sleep and increased total sleep time. REM density increased and stage 1 decreased with OLA.	None listed.	OLA may increase slow wave sleep and total sleep time in schizophrenia.
Sharpley et al. (2000)	33–60	Healthy subjects	One-dose crossover RCT. OLA 5 mg/day vs. OLA 10 mg/day vs. placebo. $N = 9$.	OLA substantially increased slow wave sleep, by 59.1% and 83.3% for the 5 and 10 mg/day doses, respectively. OLA increased total sleep time.	None listed.	OLA increases slow wave sleep and total sleep time in healthy subjects.

et al., 1999; Sharpley et al., 2000), although this effect has not been confirmed in patients with insomnia. There is also evidence that olanzapine may be useful in 1) the treatment of insomnia associated with PTSD (Jakovljević et al., 2003) based on a case series and 2) paradoxical insomnia, based on a case report (Khazaie et al., 2010) and a randomized, open-label trial (Khazaie et al., 2013).

B. Quetiapine

1. Mechanism of Action. Quetiapine, a dibenzothiazepine derivative, is the atypical antipsychotic that displays the lowest D_2 affinities (Richelson and Souder, 2000; Comai et al., 2012b). It shows antagonism at multiple neurotransmitter receptors, mainly 5-HT_{2A}, 5-$HT_{2c,}$ H_1, and D_2 (Table 1). Its sedative and hypnotic properties are attributable to its antagonism of the histamine H_1 receptor and various serotonin receptors. In monkeys, neither acute nor chronic administration of quetiapine improved sleep efficiency, whereas the first night after discontinuation, subjects had significantly decreased sleep efficiency and increases in nighttime activity (Brutcher and Nader, 2015).

2. Indications. Quetiapine is FDA approved for the treatment of schizophrenia in adults and adolescents, the treatment of bipolar mania in children and adolescents, and the treatment of bipolar depression in adults. Clinical studies examining the hypnotic effects of quetiapine are detailed in Table 15.

3. Pharmacokinetics. Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations within 1.5 hours (US FDA, 2017). The drug is 83% bound to serum proteins (DeVane and Nemeroff, 2001). Administration with food increases C_{max} and AUC by 25% and 15%, respectively. The drug is mainly eliminated through hepatic metabolism, specifically CYP3A4, and its mean terminal elimination half-life is 6 hours. Oral clearance is reduced by 40% in subjects greater than 65 years of age, although sex does not affect its pharmacokinetics.

4. Results in Insomnia Disorder. One RCT was identified in patients diagnosed with primary insomnia (Tassniyom et al., 2010). Surprisingly, although observational evidence suggests that atypical antipsychotics like quetiapine are increasingly prescribed for insomnia, the 2010 study was the only RCT that was found in the literature of an atypical antipsychotic in primary insomnia, and it had a small sample size of only 13 patients who completed the study (Tassniyom et al., 2010). In the RCT, quetiapine 25 mg/day treatment was not significantly superior to placebo at increasing sleep time and reducing latency to sleep, although there was a trend toward the superiority of quetiapine (Tassniyom et al., 2010).

In contrast, an open-label trial of quetiapine 25–75 mg/day found that the drug was effective at reducing symptoms of insomnia, increasing total sleep time and reducing PSQI (Wiegand et al., 2008).

5. Other Results. Eleven other studies of quetiapine that included sleep parameters were identified: five were open label (Juri et al., 2005; Todder et al., 2006; Baune et al., 2007; Pasquini et al., 2009), three were randomized, placebo-controlled trials (Cohrs et al., 2004; Garakani et al., 2008; McElroy et al., 2010), one was a review (Anderson and Vande Griend, 2014) pooling many of the studies cited here, one was a naturalistic study (Šagud et al., 2006), one was a post hoc analysis of two RCTs (Endicott et al., 2008), and one was a retrospective study (Terán et al., 2008).

One RCT in 14 healthy male subjects found that quetiapine 25 and 100 mg/day significantly improved sleep induction and sleep continuity under standard and acoustic stress conditions (Cohrs et al., 2004). Active treatment with quetiapine also increased total sleep time, sleep efficiency, and subjective sleep quality.

In contrast to the results of the RCT in primary insomnia, the open-label studies in other conditions were generally positive, although they were conducted in a wide range of patient populations. The included studies analyzed patients diagnosed with Parkinson's disease, treatment-resistant depression, bipolar disorder, breast cancer with tamoxifen-induced insomnia, and insomnia induced by detoxification from substance abuse. Unfortunately, a retrospective chart review (N = 43) found that quetiapine prescribed for insomnia at a mean dose of 120.3 ± 58.6 mg/day had adverse metabolic side effects (Cates et al., 2009). However, neither the RCT of quetiapine 25 mg/day study (Tassniyom et al., 2010) nor the open-label trial of quetiapine 25–75 mg/day (Wiegand et al., 2008) reported the rate of metabolic side effects, and the retrospective review did not perform subgroup analysis of the patients taking 25 mg/day (N = 4 at baseline).

6. Conclusion. A summary of the effects of quetiapine on sleep architecture is presented in Table 2. There is moderate evidence that quetiapine is not significantly effective for the treatment of primary insomnia, based on one small RCT (Tassniyom et al., 2010). Randomized studies support the usefulness of quetiapine in insomnia that is secondary to conditions for which quetiapine has an FDA-approved indication, like bipolar depression or unipolar depression (as augmentation). There is Level 1b evidence based on two RCTs (Calabrese et al., 2005; McElroy et al., 2010) that quetiapine is effective in the treatment of insomnia secondary to bipolar depression. There is Level 1b evidence based on one RCT (Garakani et al., 2008) and three open-label trials (Šagud et al., 2006; Todder et al., 2006; Baune et al., 2007) that quetiapine as augmentation of antidepressants is effective in reducing symptoms of insomnia in treatment-resistant depression.

TABLE 15
Summary of studies assessing the effects of quetiapine (QTP) on sleep

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Anderson and Vande Griend (2014)	Varied	Varied	Review of the literature of quetiapine in the treatment of insomnia.	Varied	Given QTP's adverse effects profile (see RCTs above), QTP's benefits have not been proven to outweigh the risk.	Robust studies evaluating quetiapine for insomnia are lacking.
Baune et al. (2007)	Males: mean 48.6, S.D. 12.9; Females: mean 50.5, S.D. 13.2	Treatment-resistant unipolar or bipolar II depression	4-wk open-label in-patient trial of QTP augmentation of venlafaxine or escitalopram. Mean QTP dose 340 mg/day, max 800 mg/day. $N = 27$.	PSQI total score was 8.8 ± 2.8 at baseline and 5.2 ± 1.8 at week 4, $P = 0.00$. PSQI daytime sleepiness was 1.9 ± 0.8 at baseline and 0.8 ± 0.7 at week 4, $P = 0.00$.	During the 4-wk study, neither adverse metabolic or clinical events nor significant weight gain were recorded.	QTP is effective at reducing symptoms of insomnia in patients with depression.
Calabrese et al. (2005)	18–65	Type I or Type II bipolar depression	8-wk RCT. QTP 300 vs. 600 mg/day vs. placebo. $N = 542$.	Sleep difficulties were moderate to severe at baseline. PSQI total score at last assessment improved by 5.16 points with QTP 300 mg/day and 5.46 points with QTP 600 mg/day, compared with 2.94 points for placebo, $P < 0.001$ for both dosages relative to placebo.	QTP 600 mg/day experienced 1.6 kg of weight gain vs. 1.0 kg in the 300 mg/day group and 0.2 kg in the placebo group. Mean change in fasting glucose was 6 ± 17 mg/dl in QTP 600 mg/day, 3 ± 13 mg/dl in QTP 300 mg/day, and 4 ± 26 mg/dl in the placebo group.	QTP is effective at reducing symptoms of insomnia in bipolar depression.
Cohrs et al. (2004)	19–33	Healthy subjects	Nine-night RCT. Three study periods lasting 3 days, with a 4 day washout. QTP 25 mg/day vs. QTP 100 mg/day vs. placebo. $N = 14$.	Both doses QTP significantly improved LOS and sleep continuity under standard and acoustic stress conditions. Total sleep time and SE increased.	Significant increase in periodic leg movements was observed with QTP 100 mg/day.	QTP increases sleep in healthy volunteers.
Garakani et al. (2008)	18–65	Major depressive disorder	8-wk RCT. QTP 25–100 mg/day + fluoxetine 20–40 mg/day vs. placebo + fluoxetine. $N = 114$.	Mixed-effect regression models show that QTP+fluoxetine group improved significantly more rapidly on insomnia scores. From baseline to first follow up visit, $P = 0.00055$; to second follow up visit, $P = 0.0004$; to third follow up visit, $P = 0.01$.	Sedation was more prevalent in the QTP +fluoxetine group, $P = 0.006$.	QTP is effective in reducing symptoms of insomnia in patients with depression.
Keshavan et al. (2007)	QTP group: mean 36.1, S.D. 9.8	Schizophrenia	Cross-sectional, QTP 313.33 ± 228.71 mg, vs. risperidone 3.25 ± 2.12 vs. neuroleptic-naïve patients. $N = 39$ (patients already stabilized on QTP or risperidone), $N = 31$ (neuroleptic-naïve patients)	REM counts were elevated in the QTP than in neuroleptic-naïve patients. QTP and risperidone treated patients had more prominent SWS and % of stage N2, and reduced REM sleep than never-treated schizophrenia subjects.	Not analyzed.	QTP suppresses REM sleep in patients with schizophrenia. Its therapeutic significance requires further investigation.
Juri et al. (2005)	Mean: 67.6, S.D.: 8.4	Parkinson's disease without psychosis with insomnia	12-wk open-label trial. Mean QTP dose 31.9 mg/day, range 12.5–50 mg/day. $N = 14$.	PSQI reduced by mean ± S.D. 3.8 ± 3.9, $P < 0.01$. SOL reduced from 82 ± 65.4 minutes to 28.6 ± 22.7 on last visit, $P < 0.05$.	Two discontinuations due to restless legs syndrome that worsened since the beginning of treatment. Two subjects also reported worsened sleepiness during the day. No worsening of motor symptoms or orthostatic symptoms.	QTP is effective at reducing symptoms of insomnia in Parkinson's disease patients with insomnia.

(*continued*)

TABLE 15—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
McElroy et al. (2010)	18+	Type I or Type II bipolar depression	8-wk RCT. QTP 300 mg/day vs. QTP 600 mg/day vs. paroxetine 20 mg/day. $N = 740$.	MADRS item 4 (reduced sleep) improved significantly more in both QTP arms than in placebo. In contrast, the paroxetine arm was not significantly superior to placebo in reducing item four scores.	AEs leading to treatment discontinuation were reported in 9.1% of QTP 300 mg/day, 12.3% of QTP 600 mg/day, 13.2% of paroxetine, and 8.1% of placebo. Incidence of serious AEs lowest in QTP 300 mg/day, while those treated with paroxetine displayed the highest.	QTP is more effective than paroxetine at reducing symptoms of insomnia in bipolar depression.
Pasquini et al. (2009)	19–65	Breast cancer with insomnia induced by tamoxifen	Retrospective open-label trial. QTP dose <200 mg/day. $N = 6$.	Weight increased by 4.9 pounds ($P = 0.037$). BMI increased by .Eight points ($P = 0.048$). There were no significant differences between baseline and endpoint metabolic parameters when examined by baseline BMI, age category, psychiatric diagnosis, or concomitant psychotropic medication.	Reported side effects included weight gain ($N = 2$) and dizziness ($N = 1$).	QTP increases weight gain in patients treated for insomnia.
Robert et al. (2005)	49–68	Sleep disturbances in combat veterans with DSM-IV PTSD	6-wk open-label trial. QTP mean 100 ± 70 mg/day, range 25–300 mg/day. $N = 19$.	Global PSQI scores decreased significantly, 15.82 ± 2.72 at baseline to 7.89 ± 5.15 at week 6, $P < 0.001$. Sleep quality improved, $P = 0.006$. Sleep latency improved, $P = 0.002$. Total sleep time increased from 4.0 ± 1.0 to 6.0 ± 1.8 h per night, $P < 0.001$.	Sedation was reported by 36.8% of patients, leading to discontinuation in one patient.	QTP may reduce symptoms of insomnia in patients with PTSD.
Šagud et al. (2006)	18+	Treatment-resistant DSM-IV depression	20-wk open-label trial of QTP as augmentation of antidepressants. Mean QTP dose 315 mg/day. $N = 14$.	QTP significantly improved the anxiety and insomnia subscales of the HAM-D. Insomnia scores of HAM-D was significantly reduced from baseline after 20 wk of treatment, $P < 0.05$.	Three patients had hypotension and two had daytime sedation, transient and mild.	QTP is effective in reducing symptoms of insomnia in patients with depression.
Tassniyom et al. (2010)	25–62	Primary insomnia by DSM-IV	2-wk RCT. QTP 25 mg/day vs. placebo. $N = 16$.	Increases in sleep time: placebo = 72.24 minutes vs. QTP = 124.92 minutes ($P = 0.193$). Reductions in SOL: placebo = 23.72 minutes vs. QTP = 96.16 minutes ($P = 0.070$). Trend for improvement was shown though did not react significant difference.	Two patients in QTP group reported dry lips, dry tongue, and morning drowsiness.	QTP may be effective at reducing symptoms of insomnia.
Terán et al. (2008)	NS	Insomnia during detoxification in substance abusers	Retrospective chart review. QTP 25–225 mg/day. $N = 52$ medical records.	Global Spiegel Sleep Questionnaire (SSQ) scores significantly improved throughout the 60-day follow up period, $P < 0.001$. Greatest improvement occurred in first week of treatment and remained constant thereafter.	No patients dropped out due to AEs. Most common AE was dry mouth (34.6%).	QTP is effective at reducing symptoms of insomnia during detoxification from substance abuse.

(*continued*)

TABLE 15—*Continued*

Study	Age	Diagnosis	Design + Number of Participants	Results	Adverse Events	Conclusion
Todder et al. (2006)	21–76	Treatment-resistant unipolar or bipolar depression compared with healthy controls	4-wk open-label follow up study of QTP augmentation of antidepressants. QTP 50–800 mg/day. $N = 54$.	Objective actigraphic sleep analysis: no significant difference was found between Weeks 1 and 4. SE did not change. Actual sleep time was higher at all time points in patients compared with controls, however, SOL was significantly higher in controls compared to patients. Subjective sleep analysis with PSQI: statistically significant improvements of total sleep score, quality of sleep, daytime sleepiness, between the week before admission, Week 1, and Week 2. SOL improved between Weeks 1 and 4.	Not analyzed.	QTP may be effective at reducing symptoms of insomnia in patients with depression.
Wiegand et al. (2008)	NS	Primary insomnia	6-wk open-label study. QTP 25–75 mg/day. $N = 18$.	Total sleep time (minute) increased from 358.0 ± 61.4 at baseline to 395.6 ± 62.3 at 6 w, $P = 0.03$. SOL (minute) was 22.1 ± 17.0 at baseline and 24.2 ± 19.0 at 6 wk ($P = 0.83$). PSQI total score was reduced from 13.1 ± 2.3 at baseline to 6.8 ± 3.3 at 6 wk, $P = 0.00$.	Dry mouth and transient hangover symptoms were recorded most frequently.	QTP is effective at reducing symptoms of insomnia.

IX. Discoveries, Novel Pathways, and Pipelines

The discoveries and pipelines in this section, constructed using data from a custom search of the Cortellis database, are an up-to-date (as of February 2017) snapshot of the current state of the research and development of insomnia medications.

A. Discoveries

1. Adenosine Receptor Agonist. YZG-331 is a promising sedative hypnotic and adenosine analog that exerts its effects by binding to the adenosine receptor. (See the *Other Receptors* section for a review of the pharmacology of A_{1A} and A_{2A}.)

2. Casein Kinase-1δ/ε. The casein kinase-1δ and casein kinase-1ε proteins are essential elements of the molecular oscillators known as circadian clocks (Lee et al., 2009). Their importance to the functioning of the mammalian circadian rhythm has spurred interest in casein kinase-1δ/ε inhibitors as potential clinical treatments of sleep disorders and other central nervous system disorders including neurodegenerative conditions (Perez et al., 2011).

3. Selective Melatonin MT_2 Receptors. Studies on melatonin MT_1 knockout, MT_2 knockout, and double MT_1-MT_2 knockout mice have demonstrated that these two receptors have opposing or complementary functions. Whereas MT_2 receptor activation promotes SWS, MT_1 decreases SWS and increases REMS (Ochoa-Sanchez et al., 2011; Ochoa-Sanchez et al., 2014). This evidence prompted the development of novel selective MT_2 agonists as hypnotics. The compound UCM765 has greater MT_2 receptor affinity ($pK_i = 10.18$) than melatonin ($pK_i = 9.59$) and has about 100-fold higher affinity for the MT_2 receptor than for the MT_1 receptor ($pK_i = 8.28$). UCM924 also displays MT_2 affinity ($pK_i = 10.2$) that is 300-fold higher than for MT_1 ($pK_i = 6.75$), with an intrinsic activity for MT1: IA_r-h$MT_1 = 0.1$; and for MT2: IA_r-h$MT_2 = 0.4$ (Rivara et al., 2009).

Both UCM765 (Ochoa-Sanchez et al., 2011) and UCM924 (Ochoa-Sanchez et al., 2014) increase SWS during the inactive phase of the day, without significant change in REMS or sleep architecture. The congener nonselective MT_1-MT_2 receptor UCM971 did not alter the 24-hour duration of wakefulness, NREMS, or REMS, but modified the number of episodes. MLT decreased (−37%) the latency to the first episode of NREMS and enhanced the power of NREMS delta band (+33%), but did not alter the duration of any of the three vigilance states or modify the duration of SWS (Ochoa-Sanchez et al., 2014). These data confirm the importance of targeting the MT_2 receptor for hypnotic effects. UCM765 and UCM924 show a good safety profile and are currently under development for clinical studies.

4. Selective Orexin-2 Antagonist. Although dual orexin receptor antagonists like suvorexant are effective at promoting sleep, selective orexin-2 receptor

blockers may preserve sleep architecture to a greater extent than dual antagonists (Bonaventure et al., 2015). Indeed, only orexin-2 but not orexin-1 is involved in the regulation of sleep (Dugovic et al., 2009). JNJ-42847922 is a novel orexin-2 antagonist shown to reduce the latency to NREM sleep and increase NREM sleep in the first 2 hours after administration, without affecting REM sleep in rats (Bonaventure et al., 2015). Importantly, the compound has been shown to reduce time to sleep onset and increase total sleep time after 7 days of chronic dosing (30 mg/kg). The compound did not produce conditioned-place preference or increase dopamine release in the nucleus accumbens, indicating that it lacks intrinsic motivational properties, in contrast to zolpidem. In a Phase I study in healthy human subjects, JNJ-42847922 (10–80 mg/day) significantly increased somnolence: 22 of 26 subjects (85%) receiving JNJ-42847922 reported somnolence as an adverse event, whereas only 3 of 13 subjects (23%) receiving placebo did (Bonaventure et al., 2015). The compound's pharmacokinetic profile in humans was favorable, with a half-life of 2 hours. One subject reported experiencing sleep paralysis after receiving the 80 mg/day dose.

B. Pipelines

1. Lumateperone. Lumateperone is a mechanistically novel investigational antipsychotic drug with a unique pharmacological profile, showing very high 5-HT_{2A} blocking activity (K_i = 0.54 nM) relative to its D_2 modulating activity. The drug has a 60-fold difference between its affinity for $5HT_{2A}$ and D_2 receptors compared with a 12-fold difference for risperidone, a 12.4-fold difference for olanzapine, and a 0.18-fold difference for aripiprazole (Davis et al., 2015; Snyder et al., 2015). Lumateroperone functions as a modulator of the D_2 receptor by partially agonizing presynaptic D_2 receptors and antagonizing postsynaptic D_2 receptors (K_i = 32 nM) (Snyder et al., 2015). Furthermore, the drug blocks the serotonin transporter with strong affinity (K_i = 62 nM) while having no affinity for the H_1 histaminergic or muscarinic receptors (Snyder et al., 2015). Importantly, the drug's D_2 and SERT occupancy increase with dose (Davis et al., 2015); at low doses, the drug theoretically functions as a selective 5-HT_{2A} blocker.

The company, Intra-Cellular Therapies (New York, NY), suggests on their website that lower doses of lumateperone could be useful in the treatment of sleep disorders, whereas higher doses are targeted to neuropsychiatric disease. A Phase 2 study (N = 18) of lumateperone as a treatment of insomnia characterized by sleep maintenance difficulties was discontinued early when the investigators found robust evidence of efficacy, with increased SWS and decreased wake after sleep time by polysomnography (Intra-Cellular Therapies, 2009). Furthermore, lumateperone did not impair next-day cognition as measured by Leeds Psychomotor Battery, Digit Symbol Substitution Test, or Word Pair Associates Test.

2. Piromelatine. Piromelatine is a unique drug that combines agonist activity at MT_1 and MT_2 with agonism at 5-$HT_{1A/1D}$ receptors (Laudon et al., 2012). Piromelatine was shown to have both hypnotic and antinociceptive effects by electroencephalogram (EEG) recordings and an animal model of neuropathic pain, partial sciatic nerve ligation (Liu et al., 2014). The drug was found to increase NREM sleep and decrease wakefulness in partial sciatic nerve ligation mice. Finally, the investigators demonstrated that the effect could be blocked by preadministration of a melatonin receptor antagonist, a 5-HT_{1A} receptor antagonist, or an opiate receptor antagonist (Liu et al., 2014), implicating these receptors in the mechanism of action of the drug.

In 2013, Neurim Pharmaceuticals (Tel-Aviv, Israel) announced positive results from a phase II randomized clinical trial (N = 120) of piromelatine in primary insomnia (Neurim Pharmaceuticals, 2013). Active treatment with piromelatine 20 or 50 mg/day over 4 weeks resulted in significantly improved wake after sleep onset, sleep efficiency, and total sleep time. The Clinicaltrials.gov database lists a study currently recruiting patients entitled Safety and Efficacy of Piromelatine in Mild Alzheimer's Disease Patients (ReCOGNITION); it also lists a completed study entitled The Effect of Neu-P11 on Symptoms in Patients with D-IBS. These studies indicate that Neurim Pharmaceuticals is exploring piromelatine's potential efficacy in myriad conditions, including irritable bowel syndrome and Alzheimer's disease.

X. Conclusions

In the last 20 years, preclinical and clinical research on sleep has expanded tremendously. The study of knockout mice for specific receptors has generated novel scientific knowledge of the unique role of each receptor in the regulation of sleep, the application of optogenetics to the study of sleep has elucidated new circuits, and the discovery of clock genes has generated insight into the cellular and molecular mechanisms that regulate sleep homeostasis.

In parallel, clinical studies have investigated how sleep architecture is differentially impaired in various neuropsychiatric diseases (including major depressive disorder, posttraumatic stress disorder, and Alzheimer disease) and the manner in which selective receptors' ligands can improve sleep quality and quantity.

Despite these advancements, BZDs continue to be widely prescribed, although their use, particularly in the elderly, is associated with an increased risk of falls, fractures, and emergency hospitalizations. Most or all BZDs and Z-drugs are available as generic drugs; as such, they are available to providers (private insurance companies, universal governmental health care

systems) for a very low cost compared with innovative hypnotics (Tannenbaum et al., 2015; Goreveski et al., 2012). Innovative drugs cannot compete with the price of BZDs, discouraging academia and pharmaceutical research companies from investing in sleep medicine. Clinicians resort to prescribing drugs off-label, although these compounds often lack a strong evidence base for their use.

Substantial opportunity remains for pipelines that target the unmet needs in the insomnia market. Medicines with comparable efficacy and improved long-term safety would hold a competitive advantage over current first-line therapies, especially hypnotic without cognitive side-effects or not causing motor impairments the next day. Similarly, drugs that improve sleep quality by augmenting SWS would be viewed favorably by physicians. Moreover, drugs that selectively improve sleep in specific diseases would be also a new avenue for a personalized medicine.

Advancing drug discovery for insomnia and sleep disorders requires that the industry, in collaboration with regulatory authorities, clinical experts, and patient communities, engage in promoting and requiring better treatment of this condition. Moreover, there is a need to better define and agree on the nosology of sleep-related illnesses: the classifications of patient populations and the types of outcomes, other than sleep parameters, to be monitored among clients. Research into novel hypnotics may bolster the growing conception that sleep disorders are an integral part of, rather than secondary to, diseases such as depression and Alzheimer's (Wafford and Ebert, 2008). Since the burden of insomnia and sleep disorders will likely increase in coming decades due to the aging of the population and the growing use of computer technologies (Fossum et al., 2014), research on novel hypnotics should be considered a priority.

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Wrote or contributed to the writing of the manuscript: Atkin, Comai, Gobbi.

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