

## Advances in the management of insomnia

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### Abstract

Insomnia is highly prevalent and associated with considerable morbidity. Several very efficacious treatments, both pharmacologic and non-pharmacologic, exist for the management of insomnia. New modes of delivery and new formulations of existing sedative-hypnotic medications have been introduced. Novel agents are still being developed and tested to arrive at a hypnotic that has limited side effects while still being efficacious. Innovations with respect to behavioral interventions, which are drastically under-utilized, have focused mainly on making these interventions more widely available through dissemination efforts, briefer formats and more accessible platforms.

### Introduction

Insomnia presents a significant challenge to the health and wellness of individuals receiving treatment across a diverse array of settings. In a given year, approximately 10% of the world's population will report that they suffer from chronic or persistent insomnia [1-3]. These difficulties are even more prevalent in groups such as primary care patients [4], those with physical or mental health conditions [5], and the elderly [6]. In addition, insomnia is associated with worsened physical and emotional health, including higher risk for cardiovascular disease [7], depression [8], suicidal thoughts and behaviors [9], and diminished quality of life [10].

Individuals have attempted to manage insomnia with a variety of remedies including prescription medications, alcohol, herbal supplements, and over-the-counter sleep aids, with off-label medications being used almost as frequently as those approved for the treatment of insomnia [11]. In addition to these pharmacologic approaches, a number of non-pharmacologic approaches exist for the management of insomnia. Both types of approach have their place in the management of this

sleep disorder; each has empirical support and each has shortcomings.

### “Older” sedative-hypnotic medications

Barbiturates (e.g. butabarbital, secobarbital) were prescribed by physicians for much of the 20<sup>th</sup> century, but their frequency of use slowed in favor of better tolerated benzodiazepines (e.g. flurazepam hydrochloride, quazepam, triazolam) and other medication classes. Benzodiazepines can produce significant short-term gains, such as decreased sleep onset latency and fewer nighttime awakenings [12]. However, these medications can also produce significant side effects including cognitive impairment, dizziness, morning sedation, and dependence [13].

Off label use of medications, without a US Food and Drug Administration (FDA) indication for the treatment of insomnia, is common [11]. Such agents are prescribed given their sedating side effects. They are typically prescribed for insomnia at lower doses than for their indicated uses. The most common of these are sedating antidepressants (e.g. trazodone, amitriptyline), and

atypical antipsychotic medications (e.g. quetiapine, risperidone, olanzapine).

Similarly, over-the-counter sleep aids are based on the sedating side effect of antihistamines. The active ingredient is typically diphenhydramine or doxylamine, both first generation histamine H<sub>1</sub> antagonists. Rapid tolerance to the sedative effects of diphenhydramine has been noted within four days of starting a 50 mg dose of diphenhydramine [14]. For this reason, the routine use of diphenhydramine to treat chronic insomnia is not recommended.

### **“Newer” sedative-hypnotic medications**

Following the introduction of zolpidem for insomnia in France in 1988 and its FDA approval in 1992, non-benzodiazepine, benzodiazepine receptor agonists (BZRAs e.g. zolpidem, zaleplon, zopiclone, and eszopiclone) became the most commonly prescribed medication class for managing insomnia [15]. These newer BZRAs target the gamma aminobutyric acid (GABA) type A receptor complexes and have preferential affinity for the  $\alpha$ -1 subunit (or the  $\alpha$ -3 subunit in the case of eszopiclone) over the other receptor subunits [16,17]. It is not known whether this selective binding leads to fewer cognitive and psychomotor side effects than benzodiazepines, which do not have such binding specificity.

Each of these newer BZRAs has a slightly different half-life, affording clinicians the option of matching medication to individual insomnia presentation, such as sleep onset insomnia (trouble falling asleep) and sleep maintenance insomnia (trouble staying asleep). Zaleplon has the shortest half-life (~1 hour) making it useful for presentations of sleep onset insomnia. Zolpidem also has a short half-life in immediate release formulations (1.5 to 2.4 hours) useful for sleep onset insomnia, whereas an extended release formulation (2.8-2.9 hour half-life) is intended for both sleep onset and sleep maintenance insomnia. Eszopiclone, the single isomer of zopiclone, has a 6-9 hour half-life, making it appropriate for both onset and maintenance insomnia.

The popularity of the newer BZRAs is, in part, owing to their comparable efficacy to benzodiazepines, combined with shorter half-lives and their potentially more limited side effect profile. As recently reviewed [18], common adverse effects include headache, dizziness, nausea, somnolence, fatigue, and, with respect to eszopiclone, an unpleasant or metallic taste. Although some long-term trials (e.g. 12 months) have not found evidence of tolerance, dependence or rebound insomnia [19], these remain concerns with long-term use of the newer BZRAs [18]. A meta-analysis concluded that, although indirect

comparisons suggest that newer BZRAs were safer than older medications, all hypnotic classes evaluated pose a risk of harm [20]. These authors also note that safety data in vulnerable populations like the elderly are lacking. Finally, there is concern about the association of hypnotic use with considerable morbidity and mortality [21-26].

Ramelteon is the last of the “newer” sleep medications, receiving FDA approval in 2005. It does not act upon the GABA system, but is a melatonin receptor agonist that selectively binds to MT<sub>1</sub> and MT<sub>2</sub> receptors. Similar to exogenous administration of melatonin, it has phase shifting effects on endogenous circadian rhythms [27]. It is generally well-tolerated with more effects on sleep onset, but not sleep maintenance problems [28] and, unlike the BZRAs, is not categorized as a controlled substance [29].

### **Neutraceuticals and supplements**

Despite some early indications of the promise of several foods, herbs or supplements in treating insomnia, there are generally few high-quality clinical trials to support their use. Existing clinical trial data, reviews and/or meta-analyses of chamomile [30], tart cherries [31], L-tryptophan [32,33], and valerian [34,35] suggest very mixed support, at best, for their impact on insomnia. There is more consistent support, and well-designed trials, for the use of exogenous melatonin for insomnia, although the effect sizes achieved with melatonin are small [36].

### **Non-pharmacologic approaches to insomnia management**

Non-pharmacologic approaches to the management of insomnia have been available for some time and have varying degrees of empirical support as reported extensively in practice parameters [37], consensus statements [38], evidence reviews [39], and several meta-analyses [40-42]. The following brief summaries reflect the agreements across these resources. Sleep hygiene education [43], which generally consists of simple recommendations to improve sleep (e.g. exercise daily, avoid caffeine in the evening), is frequently used due to its brevity and ease of delivery, but has very limited empiric support as a stand-alone treatment [44]. Cognitive therapy [45] (e.g. identifying and challenging cognitions that interfere with sleep) has been identified as having potential utility in the management of insomnia, though additional evidence is needed for its full endorsement as a stand-alone treatment. Relaxation training [46] alone has been shown to improve several features of insomnia. Sleep restriction therapy [47], which limits the patient's time in bed to the amount of time they report sleeping,

serves to strengthen the homeostatic drive for sleep and consolidate sleep in a limited window of sleep opportunity. Based on daily self-report of total sleep time and the efficiency of using the prescribed sleep period (averaged over one week periods), the prescribed sleep window is increased in small increments. This approach has strong empirical support, though surprisingly few trials have investigated sleep restriction as a single therapy. Stimulus control therapy [48], which does not prescribe times in bed, nonetheless asks patients to limit time in bed by going to bed only when sleepy and leaving bed if unable to sleep after 15-20 minutes. It also includes instructions to remove sleep-interfering stimuli (including behaviors like watching television in bed) from the bedroom environment. It is considered the most efficacious non-pharmacologic treatment for insomnia.

Overall, with the exception of sleep hygiene, these interventions can be expected to have some efficacy when delivered as stand-alone insomnia treatments. The most efficacious non-pharmacologic insomnia treatment, however, is a multi-component intervention referred to as cognitive behavioral therapy for insomnia (CBT-I), which typically combines sleep psychoeducation, stimulus control, sleep restriction therapy, sleep hygiene, cognitive therapy and relaxation training [40-42,49]. It is customary to list increased daytime sleepiness as a potential side-effect of sleep restriction therapy, but there are no published data in this regard.

#### **Are existing insomnia treatments good enough?**

Although there are numerous evidence-based interventions available to manage insomnia, a number of shortcomings of these approaches have been identified. For instance, the efficacy of benzodiazepines, newer BZRAs and sedating antidepressants is well-established, but safety concerns remain for each of these medication classes [20].

As recently as 2013, due to the risk for morning impairment, the FDA recommended that the bedtime dose of zolpidem be lowered [50]. This follows earlier warnings for zolpidem regarding case reports of behaviors such as driving, nocturnal eating, making phone calls, or having sex while not fully awake [2,51]. And, notwithstanding some longer term trials of up to 12 months of nightly administration [18,52], concerns about long term use remain [20]. In addition, pharmacologic intervention can often occur while neglecting the behavioral and cognitive factors that contribute to insomnia. Historically, a major shortcoming of CBT-I has been the limited availability of clinicians trained in this approach [53]. In addition, the standard duration of CBT-I, whether delivered individually or in group

formats, is 6-8 sessions. Although, this can be considered brief, time-limited therapy, it still requires fairly significant patient involvement and may not be feasible to deliver in some settings, such as primary care clinics. Due to these shortcomings, modifications to existing approaches and completely novel approaches to insomnia management continue to be developed and tested.

#### **Advances in pharmacotherapy for insomnia**

One approach to advancing insomnia care has been to develop different formulations of and/or delivery systems for BZRAs. These have included oral and nasal sprays, sublingual tablets, and inhalation systems, but whether these have advanced treatment remains to be shown [54]. A similar approach was taken with respect to introducing a low-dose formulation of doxepin, an older, tricyclic antidepressant with hypnotic effects. Here, the strategy was to reduce dosages from the typical 50-200 mg range to 3 and 6 mg tablets in order to, putatively, benefit from selective antagonism for H<sub>1</sub> receptors without activity at other receptors. Two placebo-controlled trials have now demonstrated that low dose doxepin improves both sleep maintenance and early morning awakenings, with no withdrawal effects upon discontinuation [55,56].

The alternative approach is to develop novel hypnotic medications, especially those that do not target the GABAergic system. In this regard, two classes of medication in particular that have reached phase III clinical trials appear to hold some promise. These include agents specifically targeting the 5-HT<sub>2A</sub> serotonin receptor subtype (e.g. volinanserin, eplivanserin, pruvanserin) and agents targeting the orexin (also called the hypocretin) system (e.g. almorexant, suvorexant). With respect to 5-HT<sub>2A</sub> inverse agonists, compounds that have been developed have minimal affinity to dopamine, histamine and adrenergic receptors, compared to existing sedating antidepressants such as mirtazapine and risperidone. Theoretically this may lead to fewer potential side effects. Generally, these newer agents have been associated with improvement in sleep maintenance and increases in slow wave sleep [57]. Nonetheless, despite positive phase III efficacy data, eplivanserin development was discontinued in 2009. The development of esmirtazapine (the single isomer version of mirtazapine), volinanserin, and pruvanserin were also suspended. Little is known about the reasons that prompted these decisions.

The orexin system has been implicated in sleep-wake regulation [58] and particularly the maintenance of arousal [59], with important putative links to insomnia [1,60]. There is considerable interest in orexin receptor antagonism for the treatment of insomnia [61] as an alternative to increasing sedation, and therefore decreasing arousal.

Almorexant, a dual orexin receptor antagonist that blocks both OX<sub>1</sub> and OX<sub>2</sub> receptors [62-64], was the first such compound to reach phase III studies, but the almorexant program was discontinued in 2011, due to concerns about unspecified adverse effects [65]. A separate dual orexin receptor antagonist, suvorexant, has had promising results in its clinical trials [66,67]. Despite some suggestions of limited side effects on cognition [68], the maximum therapeutic dose of suvorexant (40 mg) was shown to produce cognitive and psychomotor impairment. The field now awaits whether FDA approval will be granted for a lower dose that may have a therapeutic effect without lasting morning effects. Meanwhile, a companion compound to suvorexant, MK-6096, awaits further testing [69]. Notably, all human polysomnography data from these orexin antagonists suggest that they increase rapid eye movement (REM) sleep [70], in a dose-dependent manner [71], raising concerns about symptoms related to narcolepsy, given the presence of REM abnormalities in patients with narcolepsy and the role of orexin in narcolepsy [61].

#### **Advances in behavioral treatments for insomnia**

There are very limited side effects associated with non-pharmacologic interventions for insomnia. The only exception may be the short term increase in daytime sleepiness that arises with sleep restriction therapy in the initial weeks of treatment. Instead, the long standing shortcoming in delivering CBT-I, for instance, has been a shortage of clinicians [72]. Two recent developments are making a dent in this problem. One has been a large-scale dissemination effort by the US Veterans Administration to train clinicians to deliver CBT-I [73] with preliminary evidence of the effectiveness of these clinicians now available [74]. The second advance has been to make CBT-I programs accessible *via* the internet. Here again, findings (including randomized trials) suggest that this mode of delivery is efficacious and rivals effect sizes attained in face-to-face delivery of CBT-I [75-79].

A related approach to increasing the uptake of behavioral insomnia interventions has been to develop briefer versions of these successful interventions. This includes the introduction of a "primary-care friendly cognitive behavioral insomnia therapy" which consists of only two sessions [80] and a "Brief Behavioral Treatment for Insomnia" that involves an initial 45 minute session focused on education, stimulus control, and sleep restriction followed by a booster session two weeks later [81]. Here again, both approaches have demonstrated efficacy on standard insomnia outcomes.

A unique approach to a "brief" intervention is a one session intervention called intensive sleep retraining [82],

although that one session lasts approximately 25 hours. This treatment involves acute sleep deprivation, followed by repeated opportunities to initiate sleep presented every half hour, putatively leading to counter-conditioning of learned insomnia as the patient generates multiple successful attempts at initiating sleep. In a randomized trial, patients in the intervention arm achieved significantly greater improvements in sleep onset latency, total sleep time, and sleep efficiency and these gains were maintained for 6 months [82].

Finally, although evidence supports the two pure behavioral components of CBT-I (stimulus control therapy and sleep restriction therapy), no dismantling studies of these treatments had been conducted until recently. In just such a study (n = 179) of individuals with primary insomnia, stimulus control therapy alone, sleep restriction therapy alone and combined stimulus control and sleep restriction were compared to waitlist control [83]. All conditions were associated with significant improvements relative to the control condition. The strongest effects and highest remission rates, however, were observed in the combined condition.

#### **Other recent changes relevant to the management of insomnia**

Historically, a gradual shift away from considering insomnia to be "just a symptom" towards recognizing it as a disorder occurred during the 1990s and early 21<sup>st</sup> century. The 2005 NIH consensus statement on chronic insomnia [13] hastened a shift away from the term "secondary insomnia" in favor of "comorbid insomnia" to describe insomnia that co-occurs with other conditions. The consensus document recognized that insomnia most frequently presents with other conditions. Most recently, due to the questionable relevance in clinical practice of even this distinction, the 5<sup>th</sup> edition Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [84] replaced the diagnosis of "primary insomnia" with "insomnia disorder" to specifically avoid differentiation between primary and comorbid insomnia. A similar change was made in insomnia classification in the recently published International Classification of Sleep Disorders – Third Edition (ICSD-3) [85].

These changes follow considerable (and ongoing) work documenting that insomnia presenting with one or more of a variety of conditions, from depression and post-traumatic stress disorder to chronic pain and cancer, can be managed with current insomnia treatments, either alone or in combination with interventions for the co-occurring condition(s) (e.g. [86-92]). This work also shows that sleep improvements associated with the

insomnia intervention tend to generalize to modest improvements in the co-occurring condition(s).

### Summary and next steps

Numerous efficacious interventions exist for the management of insomnia, yet the disorder remains undertreated. Pharmacologic options that are efficacious, safe and do not pose the risk of tolerance are still needed. At this point, suvorexant is the only truly “new” hypnotic likely to reach market in the next year. The development of newer agents will no doubt continue, despite setbacks in this regard. Advances in the non-pharmacologic interventions will likely continue to be in terms of addressing barriers to engagement through clinician training, brief but effective adaptations of existing approaches, and novel delivery methods. One approach that has only recently been proposed is the suggestion that insomnia treatment be delivered in a stepped care model [93,94], such that graduated levels of behavioral interventions would be provided (e.g. self-help approaches, brief interventions, standard CBT-I with a specialist). We are likely to see evaluations of this approach in the next few years. Finally, surprisingly little work has been done to test the clinical guideline that pharmacotherapy and behavioral interventions be combined [95]. One trial has demonstrated the efficacy of this approach [96], but a definitive trial that tests the efficacy of short term hypnotic use (e.g. 1-3 weeks) during the early phase of behavioral treatment would be informative.

### Abbreviations

BZRA, benzodiazepine receptor agonist; CBT-I, cognitive behavioral therapy for insomnia; FDA, US Food and Drug Administration; GABA, gamma aminobutyric acid; REM, rapid eye movement.






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Wilfred R. Pigeon was previously on the Purdue Pharma, LLP Speakers bureau for Intermezzo and receives royalties from Ivy Press, Inc. for *Sleep Manual: Training your Mind and Body to Achieve the Perfect Night's Sleep*. The authors declare that they have no other disclosures or competing interests to report.

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