The long-term management of chronic insomnia: recommendations for primary care physicians

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Insomnia is a highly prevalent condition that often becomes chronic and is associated with significant psychiatric and medical morbidity. There are several efficacious strategies for the treatment of insomnia. Historically, however, there has been little advice for the long-term management of this condition. This article: reviews the historical context for the treatment strategies currently available; previews, in a general way, the new therapies in development; and suggests reasonable practice guidelines for both the short- and long-term management of insomnia.

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Insomnia is a very common disorder with a prevalence of approximately 25% for acute insomnia and 10% for chronic insomnia. Chronic insomnia is associated with increased fatigue, cognitive impairment, mood disturbance, physical complaints and reduced quality of life.[1–4] Beyond these sequelae, there is now considerable evidence that chronic insomnia increases the risk of substance abuse,[5] psychiatric illness (especially major depressive disorder),[5–11] hypertension and/or cardiovascular disease,[12] dysregulation of glucose homeostasis,[13] immunosuppression[14] and increased mortality.[15] Despite the prevalence and consequences of allowing insomnia to go untreated, there are no best practice guidelines for its long-term management. In this review, we will provide:

- some perspective on how treatment has been conducted in the past
- information on current therapies
- an overview of novel approaches in development
- considerations for the management of chronic insomnia.

Historical context

For several decades beginning in the 1970s, insomnia was considered a 'symptom' not a 'disorder'. To the extent that insomnia was considered 'just a symptom' of medical or psychiatric disease, it was believed that the treatment of the parent disorder was sufficient and would result in the resolution of the insomnia. Long-term management of insomnia, therefore, was thought to be unnecessary.

Despite the 'only a symptom' perspective, targeted treatments were developed and evaluated. Initially barbiturates, then benzodiazepines and, most recently, a class of compounds referred to as benzodiazepine receptor agonists (BZRAs) (also known as 'non-benzodiazepines') were indicated for use as sedative hypnotics. While all three classes have demonstrated efficacy, barbiturates were shown to have a high abuse potential and a low lethal dose profile, and were also found to have what are thought to be negative effects on sleep architecture (reduced amount of rapid eye movement and slow-wave sleep). The benzodiazepine hypnotics were also thought to have similar attributes, but there is little or no evidence for these claims. Benzodiazepines bind to the benzodiazepine receptor component of the γ-aminobutyric acid (GABA) receptor chloride channel complex. The α-subunit is the main receptor site on the GABA complex and at least five α-receptor subtypes have been recognized. Most of the older benzodiazepines bind to multiple α-receptors. This nonselective binding is thought to cause their hypnotic, anticonvulsant, muscle relaxant and other CNS actions.

Despite both the clinical and market success of the barbiturates and the benzodiazepines, BZRAs gained widespread acceptance as the therapeutic standard in practice owing to the fact that this class of medication did not possess the aforementioned

negative attributes, with the exception of some questionable concerns regarding tolerance and dose escalation. The first BZRA medications developed and marketed as hypnotics were zolpidem and zopiclone, with the more recent additions of zaleplon and eszopiclone. Each medication is chemically distinct. Zolpidem is an imidazopyridine, zaleplon belongs to the pyrazolopyrimidine class and eszopiclone is a pyrrolopyrazine derivative of the cyclopyrrolone class. They all act as agonists at the benzodiazepine receptor component of the GABA receptor chloride channel complex and preferentially bind to the α_1-receptor, which is thought to explain their minimal anticonvulsant and muscle relaxant action. The selective hypnotic effect is an important advantage over benzodiazepines, particularly for elderly individuals. BZRAs are less likely to produce residual 'hangover' the next day, are safer than benzodiazepines in overdose, possess a low risk of withdrawal effects, produce no rebound insomnia and have minimal tolerance issues.

Given a dearth of long-term efficacy data on BZRAs and a pervasive belief that chronic insomnia is a symptom of depression (acute or subclinical), coupled with abundant data on the long-term efficacy and safety of sedating antidepressants, their lack of need for scheduling and their relatively low cost, many have opted to use sedating antidepressants for the long-term management of insomnia. The medications typically prescribed for this purpose are amitriptyline, trimipramine, doxepin and trazodone. This management strategy has burgeoned so dramatically that trazodone is prescribed in the USA as a hypnotic 30% more frequently than any other medication. It should be noted that this is so despite very limited evidence for its effectiveness in treating insomnia in the absence of depression[16] and no safety data whatsoever for primary insomnia.

In parallel, nonpharmacological treatments have also been developed and tested. Commonly referred to as cognitive–behavioral therapy for insomnia (CBT-I), this treatment modality has been found to be effective,[17,18] notably, to be as effective as sedative hypnotics during acute treatment (4–8 weeks),[19,20] and to be effective at sustaining improvements in sleep in the long term (following treatment).[19] Longitudinal studies provide good evidence of the sustained treatment effects of CBT-I.[18,21]

The remaining historical development of interest is that primary insomnia has once again become considered a distinct nosological entity. Both psychiatric (*Diagnostic and Statistical Manual*) and the medical (*International Classification of Sleep Disorders*) diagnosis guidelines recognize insomnia as a primary disorder (as well as recognizing the existence of secondary insomnia). These carry more weight, especially as no occult/intrinsic sleep disorder was discovered that gives rise to the symptom of insomnia.[22] Successful treatment of the medical and/or psychiatric 'parent' disorders often does not result in amelioration of insomnia,[23–26] and insomnia often becomes chronic despite the resolution of what were clearly acute medical and/or psychiatric precipitants.[27–30] More recently, a formal nosology for insomnia has been developed for research purposes.[31] This system (The Research Diagnostic Criteria for Insomnia) uses a set of definitions that may also be useful for the purposes of clinical diagnosis. Within this system, insomnia is defined in terms of insomnia disorder, primary insomnia, psychophysiological insomnia, insomnia associated with a medical illness and insomnia associated with a psychiatric illness.

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Current approaches to the long-term management of insomnia

Pharmacotherapies

At present, insomnia is considered a chronic disorder and there is no rational approach to its pharmacological management over the long term. There is no evidence that the medical treatment of insomnia results in clinical improvements that persist beyond the period in which active treatment is provided. In fact, it is generally accepted that when treatment is discontinued, insomnia recurs with equal or worse severity (depending on the medication). Given that primary insomnia is a chronic disorder and 'insomnialytics' have no effects beyond active treatment, the only remaining option for the pharmacological management of insomnia is long-term treatment or maintenance therapy. While such an approach is now the standard of practice for disorders such as hypertension and major depression, there has been a reluctance to engage a similar strategy for chronic insomnia. The major concerns are two-fold: is primary insomnia sufficiently serious to warrant long-term treatment; and are the BZRA sedatives effective in the long term without habituation and dose escalation?

As summarized above, there is now a preponderance of evidence to suggest that insomnia confers an increased risk of new onset or recurrent psychiatric and medical illness. Thus, long-term treatment

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appears to be indicated. The question of whether BZRA sedatives provide long-term efficacy without dose habituation and dose escalation has been addressed empirically, albeit in a limited way. To date, there has been one published study showing that a BZRA (zaleplon) produces clinical gains that are stable for up to 12 months.[32] Given the data from this study, it is expected that similar investigations will be conducted for the other BZRAs. Data such as these will begin to call into question the long-held assumption that long-term treatment with hypnotics is not advisable.

Assuming that the findings from the 12-month trial of zaleplon[32] can be generalized to the whole class of medications, the primary issue raised by such studies is the matter of what constitutes 'long term'. While this is an empirical question, which may continue to be incrementally answered in 6–12-month extensions to the definition of 'long term', many may suspect that therapy with BZRAs cannot be extended *ad infinitum*. If this is the case, two approaches are possible. One approach would be to extend the efficacy half-life of hypnotic treatment using an intermittent dosing regimen. While this has been shown with intermittent zolpidem for periods of up to 3 months,[33,34] it is also likely that this strategy (like its 'every night at bedtime' counterpart) cannot be used indefinitely. The remaining approach (given an appropriate dose and duration of treatment) is to use a treatment discontinuation protocol as a means to extend treatment effects beyond the therapeutic window. While this clearly represents 'good medical practice', it has not been formally evaluated.

Cognitive–behavioral therapy

At present, CBT-I is clearly indicated when the condition is chronic, or in acute cases where pharmacotherapy may pose a potential safety concern (such as in pediatric or geriatric patients, when there is a potential for drug interactions, or when patients present with a history of substance abuse). Unfortunately, these guidelines are of limited use for four reasons.

First, behavioral interventions appear to be more costly. Secondly, there is a lack of awareness among healthcare professionals about the procedures and effectiveness of behavioral medicine in general and regarding behavioral sleep medicine in particular. Thirdly, there are only a few hundred clinicians worldwide who are trained in, experienced with, and specialize in the provision of this kind of sleep medicine. Fourthly, most insurance companies and health plans (at least in the USA) do not cover CBT-I, and those that do, provide cover under mental health codes and benefits. These considerations, when taken alone or in combination, highlight a disturbing reality: most patients will not receive CBT-I.

This state of affairs, however, may change in the near future as several watershed events have occurred that may serve to make CBT-I more widely available. These include:

- the knowledge that the long-term effects of CBT-I may justify the short-term expense of therapy, especially compared with maintenance therapy using the newer generation hypnotics
- recent efforts (such as this review) to characterize chronic insomnia as a disorder which requires targeted treatment
- clear support from the American Academy of Sleep Medicine for CBT-I as a first-line treatment for insomnia
- availability of published treatment manuals and training opportunities[35,36]
- existence of an accreditation board to certify competence to provide behavioral sleep medicine services
- establishment of new billing codes enabling CBT-I services to be billed under medical practice.

While the considerations already mentioned may serve to make CBT-I more openly available, there is a remaining issue that needs to be considered; CBT-I requires substantial patient compliance. It has been suggested that noncompliance may be related to the excessive daytime sleepiness that accrues from the sleep restriction facet of CBT-I. A recent investigation has shown that CBT-I combined with daytime administration of modafinil resulted in decreased daytime sleepiness, increased compliance and no decrement in treatment efficacy.[37] Thus, this form of combined therapy may represent one strategy to increase patient acceptance of CBT-I.

New developments for long-term insomnia management

New pharmacotherapies

There are essentially two approaches to the development of new pharmacotherapies. First, modify existing BZRAs so that they produce more robust effects and/or fewer side effects. Secondly, identify new compounds that have different therapeutic targets.

The first approach is typified by the effort to create single isomer or modified-release formulations of existing medications. The single isomer strategy is to isolate the therapeutically active isomer of a racemic compound, resulting in a more potent formulation or an equally potent version with a reduced dosage. The additional promise of this strategy is that side effects are reduced by eliminating administration of the isomer that may only serve to produce nonspecific effects and the reduction in the overall dose of the medication. The modified-release strategy also addresses the issue of potency and side-effect profiles, but does so in a different manner. Before the application of this methodology, the clinician was required to match the pharmacokinetic profile of the hypnotic to the presenting complaint. For example, if the patient presented with a sleep onset problem, a short-acting hypnotic would be prescribed. If the patient presented with a sleep maintenance problem (middle- or late-night insomnia), a longer-acting hypnotic would be prescribed. While this approach has the advantage of allowing the clinician to tailor treatment to the patient's needs, it has two drawbacks. In the case of short-acting hypnotics, there is the potential for within-night rebound insomnia (similar to that which occurs with alcohol). In the case of long-acting hypnotics, there is the potential for residual daytime effects (sedation persisting beyond the sleep period). With the advent of modified-release versions of shorter-acting medications, it may be possible to extend the therapeutic window without the risk of 'hangover' effects. Put differently, the ideal formulation exerts its clinical effect rapidly, has a sustained effect for the whole of the sleep period, and is inert by the time the patient awakens. Modified release of short-acting medications allow for this ideal pharmacokinetic profile by the bi- or triphasic release of a short-acting substance.

The second approach is typified by the effort to identify and target selectively receptors or neurotransmitter systems other than those affected by standard benzodiazepine receptor agonism. Several approaches are being developed including compounds that:

- bind to non-synaptic benzodiazepine receptor sites
- directly modulate GABA
- modulate serotonin (antagonists effecting 5-HT_{2A} receptors)
- modulate melatonin (melatonin receptor agonists).

The promise of these approaches is that the effects on sleep may extend beyond improvements in sleep continuity (i.e. promote sleep initiation and maintenance) to improvements in sleep architecture. For example, one or more of the strategies identified above may promote slow-wave sleep in such a way as to provide deeper and more restorative sleep, and these effects may have the additional consequences of promoting better daytime performance.

Combined therapy may be a strategy to increase patient acceptance of CBT-I.

New approaches to dosing schedules

Data from intermittent dosing investigations[34,38] provide confirmatory evidence regarding average effects, the lack of rebound insomnia on 'nonpill' nights, the stability of clinical gains and absence of dose escalation. Of particular note, non-nightly dosing has also been successfully combined with simple behavioral instructions in the primary-care setting.[38] The data from these studies also clearly show, however, that patients, while not experiencing rebound insomnia, are predictably worse on nights when medication is not used, compared with nights when medication is used. Thus, while intermittent dosing may confer a longer efficacy half-life, the strategy has the major disadvantage of failing to provide symptom relief on 'nonpill' nights. There may yet be a way to capitalize on the intermittent dosing schedule and still provide clinical gains on nights that patients do not use medication. Specifically, the use of placebo on nonmedication nights might produce clinical gains while minimizing exposure to the active compound. Such a strategy would seek to produce clinical gains not only via the placebo response, but also by a classical conditioning effect whereby placebo, as a conditioned stimulus, is used to elicit the soporific effects conferred by hypnotics. Promising preliminary results have been found with this method across a variety of disease states.[39] Whether this will also be a useful approach for the long-term management of insomnia awaits investigation.

An ideal formulation has a rapid and sustained clinical effect, and is inert by the time the patient awakens.

New approaches to CBT-I

Apart from the possibility of combined therapy (for example, CBT-I and concomitant treatment with modafinil), new approaches to CBT-I have focused primarily on the issue of treatment delivery. These new approaches include:

- shortening the length of treatment from six to eight sessions in a tertiary-care setting to two to four treatment sessions in a primary-care setting[40]
- training and accreditation of clinicians who are expert in the provision of cognitive and/or behavioral treatment in the delivery of CBT-I

- training non-MD or PhD healthcare professionals to deliver the treatment[41]
- deploying internet- and phone-based clinician-guided CBT-I.[42]

Specific recommendations for the primary care physician

Attend to acute presentation

Although the focus of this article is the long-term management of chronic insomnia, it should be emphasized that aggressive treatment of acute insomnia may constitute the 'ounce of prevention' that obviates the need for 'a pound of cure'.

While the majority of instances of acute insomnia appear to resolve spontaneously, a large minority of acute episodes persist. Moreover, once chronic, very few episodes of insomnia resolve spontaneously. This suggests that early intervention is desirable. This may be accomplished either with medication (ideally BZRAs or next-generation hypnotics) or with some simple behavioral recommendations. With respect to the latter, it may be useful to recommend to that:

Intermittent dosing schedules have shown benefit.

- the patient avoids using increased amounts of alcohol to induce sleep
- following a night of poor sleep, the patient does not sleep in on the following day or retire early on the next evening
- the patient avoids napping or, following a nap, delays bedtime by an equivalent amount of time
- when awake, the patient should not spend protracted amounts of time in bed (i.e. >5–15 minutes)
- insomnia, especially in association with life stressors, may be an adaptive process to the extent that there is more time in the day to resolve issues
- insomnia in the short term is likely to resolve but, if the problem persists for more than 1–2 weeks, there are a variety of safe and effective medications that can be prescribed.

The physician prescribing in the short term should consider: matching the half-life of the medication prescribed to the specific complaint (i.e. early, middle or late insomnia); a treatment plan that specifies the duration of treatment; and planned follow-up appointment(s) to reassess the insomnia complaint.

Long-term guidelines

The same practices outlined above also apply to the physician considering long-term management of insomnia with pharmacotherapy. In addition, the following recommendations are made.

- The presence of any comorbid medical or psychiatric conditions is assessed and, if identified, treated. Two important things should be noted.
  - it is not necessary, and perhaps not advantageous, to delay the targeted treatment of the insomnia because of another disorder.
  - other sleep disorders, such as restless legs syndrome (RLS) and obstructive sleep apnea, may serve to precipitate or perpetuate insomnia. Thus, the diagnosis of RLS, for instance, does not rule out the possibility of concomitant insomnia (and vice versa). Both conditions require treatment.
- CBT-I, if available, should be the first-line treatment before proceeding to pharmacotherapy in the long term, or if pharmacotherapy has been deployed with little or no success.
- Follow-up should be scheduled to assess efficacy, dose escalation and side effects.
- Use of a fixed intermittent dosing schedule (rather than 'as-needed' use) should be considered.
- Once the insomnia complaint has ameliorated and is stable with medication, a taper schedule should be designed and attempted. The inclusion of behavioral instructions for relapse prevention may greatly assist this process.

Conclusion

Given that acute and chronic insomnia warrant targeted treatment, it should be of some comfort to know that there is currently a diversity of treatment options available, that there is a virtual flurry of ongoing research both with respect to the pathophysiology of insomnia and its treatment, and that in the very near future novel approaches will be available.

Key messages

- Early treatment of insomnia is desirable.
- Medication (a BZRA or next generation hypnotic) or simple behavioral therapy should be initial treatment of insomnia.
- Long-term treatment of insomnia should be CBT-I in the first instance, followed by pharmacotherapy.

After reading this article you will be able to:

1) Understand the need for early and targeted pharmacological and/or behavioral therapy in chronic insomnia
2) Apply strategies to aid the optimal management of chronic insomnia

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