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PRO/CON DEBATE

Hypnotics Should be Considered for the Initial Treatment of Chronic Insomnia

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Insomnia is the most common sleep disorder and substantial data establish the adverse effects that occur when this condition remains untreated. As a result, it is important that effective therapies are developed, empirically validated, and administered clinically. Currently, there are a number of insomnia therapies differing substantively in their attributes, that have been demonstrated to be effective in controlled clinical trials. These different attributes determine their suitability for use in particular patients and clinical settings. The present debate addresses one such circumstance, the initial treatment of chronic insomnia, and considers the relative suitability of therapies in terms of two broad categories, pharmacologic and behavioral treatment. In this article we will argue that pharmacological treatment with hypnotic agents is a viable initial treatment of chronic insomnia and in some individuals is the preferred initial form of therapy. As a basis for this argument we will briefly discuss the strengths and weakness of these broad categories of therapies.

Addressing the question of interest necessitates that the attributes of two large classes of therapies be compared. Both of these classes, pharmacologic and behavioral therapies, are comprised of a heterogeneous group of treatments that vary greatly among themselves in important properties.[1] It is, therefore, important to bear in mind that it is not reasonable or desirable to characterize all of the therapies that compose these groups as possessing a single attribute, or set of attributes. For example, many properties vary among the benzodiazepines, and for a particular benzodiazepine as a function of dose. Bearing this limitation in mind, for the purposes of this exercise, some general statements can be made that help to frame the issues around the properties of existing therapies and that will be helpful in deciding whether and when they should be administered (See Table 1).

Among the pharmacologic therapies, this article focuses on the hypnotic agents (benzodiazepines and non-benzodiazepines) that exert their effects primarily via the benzodiazepine binding site on the GABA A receptor complex. These agents are the pharmacological therapies that are approved by the FDA for the treatment of insomnia. Other pharmacologic insomnia therapies include sedating antidepressants, anticonvulsants, and antipsychotics as well as several over-the-counter preparations (most commonly anti-histamines). The antidepressants, anticonvulsants, and antipsychotics, are used "off-label" for the treatment of insomnia. They have been approved by the FDA for use in conditions other than insomnia where they were noted to have sedation as a side-effect. Similarly, antihistamines, originally developed as treatment for allergic conditions are the primary constituent of over-the-counter sleep aids. Although these alternatives to hypnotic medications are frequently used, conclusions regarding the safety and efficacy of these agents are limited because of the paucity of placebo-controlled studies in the treatment of insomnia. For example, trazodone, one of the most widely prescribed agents for the treatment of insomnia has only been the subject of one placebo-controlled trial in primary insomnia patients.[2,3] As a result, there is no research base supporting their use in the initial or other treatment of insomnia. In contrast, hypnotic medications have been the subject of a relatively large number of placebo-controlled trials establishing their efficacy, side-effects, and attributes in the treatment of insomnia.[4]

We will contrast the attributes of the hypnotic medications in terms of suitability as initial treatments of chronic insomnia with those of behavioral therapies including stimulus control, relaxation therapy, sleep hygiene, cognitive therapy and the combination of these therapies, which, while varying in their characteristics, we refer to collectively as cognitive-behavioral therapy for insomnia (CBT). Among non-pharmacologic therapies (e.g., psychotherapy, counting sheep), CBT has the strongest empirical base supporting its efficacy.[5,6]

CHARACTERISTICS OF HYPNOTIC MEDICATIONS VS. CBT FOR INITIAL TREATMENT OF CHRONIC INSOMNIA

There are a number of attributes of hypnotics which lead them to be the preferred initial treatment of chronic insomnia in some clinical circumstances (Table 1). Below we discuss several of these attributes. The order of our list does not imply any greater or lesser importance.

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Table 1— Comparison of Properties of Hypnotics, CBT, and CBT+Hypnotics

	Hypnotics	CBT	Hypnotics +CBT	Non-Hypnotic Medications
Evidence Base Supporting Efficacy and Safety in Insomnia Treatment	+++	+++	+++	---
Speed of Response	+++	---	+++	?
Duration of Benefit in Responders	- (1)	+++	+++(2)	- (1)
Availability in Clinical Practice	+++	---	---	+++
Side-Effects	-- (3)	+++	-- (3)	---
Abuse Risk	- (5)	+++	- (5)	+++
Dependence	+ (6)	+++	+ (6)	?
Patient Responsibility to Change Behavior	+++	---	---	+++
Evidence of Efficacy for Improving Total Sleep Time	+++	---	+++	---
Use in Drug Abuse Prone Individual	---	+++	---	+++
Effective irrespective of the presence of behavioral targets	+++	--	+++	?

*The amount of time (mean +/- one standard deviation) available for analysis during the baseline portion of the evening was 137 +/- 42 minutes, and the amount of time available for analysis at the 'optimal level of CPAP' was 123 +/- 61 minutes.

(1) Following discontinuation of medication, some studies suggest that insomnia returns although we have little data addressing this issue and lack data on when to optimally discontinue medications. We have little data on nightly long-term treatment of insomnia with medications. In one study, there is evidence of sustained efficacy up to 1 year.[16]

(2) Where medications use is not contingent on sleep, there appears to be sustained benefit following medication discontinuation,[7,8] but not when taken on a contingent basis[12]

(3) Hypnotics are relatively side-effect free, however the most common side-effects include amnesia, sedation, motor impairment;

(4) Vary by medication and frequently include sedation, weight gain, sexual side-effects, sometimes significant risks in overdose, but most importantly, because of lack of studies in insomnia patients, their safety and side-effects when used in this population are unknown.

(5) Recent data suggest that in the FDA approved dosages abuse risk is low and abuse is limited to an drug-abuse prone subgroup of the population[20,21]

(6) Very little data exist on the long-term treatment of insomnia, however the data that is available does not suggest significant risk of dependence phenomena in up to 1 year of nightly treatment with eszopiclone,[16] and zaleplon,[18] and 3-months of intermittent treatment with zolpidem.[19]

Speed of Response

Hypnotic agents have a rapid onset of action, exerting a therapeutic effect on sleep on the first night of therapy. In contrast, CBT typically does exert maximal therapeutic effect until 3-4 weeks after initiating treatment.[7,8] Indeed, improvement in insomnia symptoms occurred sooner with a hypnotic medication (triazolam) than behavioral therapies in several comparative trials.[7,9,10] On this basis, it can be concluded that in cases where rapid relief of insomnia symptoms is needed or desired, hypnotic agents would be the treatment of choice for initial therapy.

Availability in Clinical Practice

Compared with CBT, hypnotic medications are much more readily available in clinical practice and can be implemented immediately.[11] Due to the need for training and the time required for implementation, medical practitioners are generally not able to administer CBT to their patients with insomnia and have to refer them to a specialist. This has several consequences, including a delay in the initiation of treatment and subsequent therapeutic response. Because of the extra step of requiring a referral, many patients may be lost to follow-up and not receive the treatment they need. These considerations further support the initial use of hypnotic medications as a means of achieving rapid and reliable improvements in sleep in patients with insomnia. In addition, the supply of well-trained specialists who are able to provide CBT is not sufficient to treat the number of patients requiring insomnia therapy. During the initial period of behavior change (e.g., initiation of regular sleep schedule, getting out of bed during bouts of wakefulness), patients may feel worse (more sleepy) than before treatment began. Without the assistance of a trained practitioner during this process, the patient may believe that CBT isn't working and quit the therapy. In this situation a hypnotic is a better treatment option than either no intervention or a failed intervention. As a result, from a practical point of view, effective CBT may be simply unavailable for many patients with insomnia necessitating initial therapy with hypnotic medications.

Minimal Patient Burden for Behavioral Change

The behavioral underpinnings of many chronic diseases are well known. Poor eating habits, a sedentary lifestyle, obesity, cigarette smoking, and alcoholism all play a role in health problems that represent a large component of the disease burden in the United States. As a result, greater attention has been focused on changing these problematic behaviors among primary care practitioners, the general population, and specialists in behavioral medicine, who have developed sophisticated behavioral interventions. The fact that these disease-promoting behaviors remain primary contributors to disease is a testament to the challenges inherent in helping patients change their behavior. Successful CBT requires that patients make a commitment to sustained effort which, for a period of time, frequently yields no improvement. The burden placed on the patient increases the likelihood that patients will elect not to pursue treatment or fail therapy. Unlike CBT, pharmacotherapy does not require the commitment to exerting a sustained effort that is required in order to make a significant change in behavior.

More importantly, a number of conditions, including those that are the most frequently associated with insomnia, interfere with the ability of affected individuals to change their behavior and engage in the tasks needed for CBT to be effective. For example, major depression is characteristically associated with impairment in energy and motivation. Changing behavior tends to be anxiety provoking in general, which presents a special challenge for

patients with anxiety disorders who tend to have difficulty making changes of any kind, which would undermine their ability to implement CBT. In addition, some individuals with insomnia have impairments in understanding, perceiving, or organizing information which would impede the capacity to effectively implement CBT, including those with schizophrenia, dementia, and mental retardation. Lastly, any of a large number of medical diseases which severely restrict activity or leave a patient bedbound render affected individuals unable to comply with many aspects of CBT. As a result, the responsibility that patients with insomnia change their behavior not only presents a challenge to effective CBT but also may eliminate this therapy as an option for some patients with insomnia associated with co-morbid conditions. In such conditions, hypnotic medications would be the preferred therapy for insomnia.

Effectiveness in the Absence of Behavioral Targets

Finally some patients may lack behaviors which are the targets of CBT. For example, some patients may have a regular sleep schedule, do not spend excessive time in bed, do not ruminate about the inability to sleep or consequences of sleep loss, use the bed only for sleeping and have a well-entrained circadian rhythm. In these cases the behavioral therapist is quite limited. A hypnotic would be an appropriate first line treatment in such a circumstance.

THE CHOICE TO USE HYPNOTIC MEDICATIONS AS INITIAL THERAPY FOR CHRONIC INSOMNIA

The above considerations suggest a number of attributes of hypnotic medications that lead them to be the preferred initial therapy for chronic insomnia in particular circumstances. These include where rapid amelioration of insomnia is needed or desired, in the many patients seen in the clinical practice of medicine where CBT is unavailable or the referral to a specialist is encumbered, in individuals who have difficulty or reluctance to change behavior or who are prevented from doing so by a disease co-morbid with insomnia, and in those who have insomnia that is not associated with the behaviors that are the targets of CBT.

Hypnotic medications may also be the preferred initial therapy for chronic insomnia by some patients, not so much because of preferred attributes of these medications but because of their attitude towards mental illness, the way they understand their disease, or a predilection for medication treatments. Some patients with insomnia simply refuse the option of CBT or prefer hypnotic medications despite a recommendation for CBT. There are some patients that appear to understand their sleep difficulty as one of somatic origin (e.g., a chemical imbalance in their brain) and have a preconceived notion that a behavioral intervention would, as a result, not address their problem. In these patients, medications are perceived as a "medical" interventions which they feel are a more appropriate treatment for their problem unlike behavioral interventions which may be seen as more psychological or mental-illness related.

THE INITIAL CHOICE OF THERAPY FOR CHRONIC VS. SHORT-TERM INSOMNIA

It is important to note that this debate specifically addresses initial therapy for "chronic" insomnia as opposed to "short-term" insomnia. This distinction may have important implications for the relative suitability of initial therapy with CBT vs. hypnotic medications. One relevant issue that remains unaddressed is whether chronic insomnia patients require chronic treatment. This only applies to pharmacotherapy because CBT is administered during one roughly 4-6 week period and, when effective, appears to lead to durable benefit.[5,6,12] In terms of pharmacotherapy, we lack systematic data on the durability of the treatment effects after discontinuation. A major limitation in this regard, is that until very recently we have had few studies of pharmacotherapy in chronic insomnia patients for longer than 4 weeks that might help to address this question.[4] Nonetheless, the available preliminary data suggest that some patients with insomnia continue to experience insomnia symptoms after pharmacotherapy is discontinued.[12] As a result, it is necessary to assume that some patients initially treated with hypnotic medications will continue to need treatment with their medication for periods much longer than 4 weeks. This raises the question of whether the prospect of longer-term treatment of insomnia with hypnotic medications should be considered a deterrent to using them for initial treatment in patients with chronic insomnia.

It has generally been assumed that the treatment of insomnia with hypnotics for longer than 3-4 weeks should be avoided.[13] There appear to be a number of factors that have promoted this long-standing clinical guideline including: the absence of treatment data beyond 4 weeks duration, the assumption that chronic insomnia is invariably a symptom secondary to a psychiatric or medical disorder which, unlike the insomnia, should be the target of treatment, the assumption that longer-term hypnotic treatment is inevitably associated with dependence (tolerance, withdrawal) and a heightened risk of abuse, and the fact that until very recently there were no medications that were approved by the FDA for an indication other than the "short-term treatment of insomnia".[1] Until recently, we have lacked empirical means to assess these assumptions. However, a number of new studies suggest that the risk-benefit ratio of longer-term treatment with some hypnotic agents is more favorable than had been assumed.

These studies suggest that:

1. Insomnia merits treatment in its' own right in that it sometimes occurs independently of any associated condition and often does not respond to effective therapy for the associated conditions;[13-15]

2. Evidence to date has indicated that the dependence risks associated with some hypnotic medications are relatively small in that neither tolerance nor significant withdrawal problems were observed in up to 1 year of nightly treatment with eszopiclone (included a 6-month placebo-controlled phase), a 1 year open-label study of zaleplon, and a 3-month study of intermittent dosing with zolpidem;[16-19]

3. There is no evidence that the abuse risk increases with duration of treatment with hypnotic medications and dose escalation by insomnia patients is infrequent.[19] Further, there is evidence that insomnia patients take their medications for therapeutic and not recreational purposes; significant abuse risk appears to be largely limited to a multi-drug abuse prone subset of the population;[20,21]

4. The FDA recently approved the medication eszopiclone with an indication for the "treatment of insomnia", without spec-

ification to duration of use.

Although these studies are relatively few, they represent an emerging empirical basis for making treatment decisions related to the longer-term use of some hypnotic medications. They are consistent in suggesting that it is reasonable to consider initial therapy of chronic insomnia patients even if therapy will be needed for as long as a year, and suggest that the risk-benefit ratio of treatment with at least some hypnotic agents in this setting is much more favorable than has been long been assumed. Clearly, further studies are needed to better address the longer-term pharmacologic treatment of insomnia. Such studies should include assessment of how and when to optimally discontinue medications and the impact of long-term use of hypnotics on sleep self-efficacy, beliefs and attitudes about sleep, and the overall longitudinal course of insomnia.

THE INITIAL USE OF HYPNOTIC MEDICATIONS AS PART OF INITIAL THERAPY IN COMBINATION WITH CBT

CBT and hypnotic medications are not mutually exclusive forms of therapy. In fact, the attributes of these two types of treatment suggest that they might be complementary therapies and it is important to consider the initial use of hypnotic medication in patients with chronic insomnia as part of combination therapy with CBT (Table 1). In particular, based on evidence that the benefits of CBT are durable[5,12] and that hypnotic medications lead to rapid improvement, the combination treatment has the potential to lead to an early and enduring therapeutic effect in insomnia patients.[22]

A combined approach, by capitalizing on the rapid improvement provided with hypnotics, may reduce the initial discomfort experienced by patients during the initial stages of CBT, which may, thereby improve adherence to the behavioral regimen and diminish dropout rate.[22] Further, meta-analytic reviews of these two types of interventions have found comparable effect sizes in reducing wakefulness during the sleep period; however, hypnotics appear to be superior in improving sleep time.[6,23] By combining hypnotics with CBT, greater improvements in total sleep time may be appreciated by patients treated with the combination than CBT alone. While several studies have examined the attributes of combined therapy vs. treatment with CBT or hypnotics alone, none of these studies has addressed the critical question of the relative speed of response of these therapies.[12,24] Considering the clinical implications of the response speed discussed above, such studies will help to better understand the potential utility of combination therapy in clinical practice and help to delineate how to optimally choose among the available therapies.

CONCLUSIONS

There are clearly a number of circumstances where hypnotic medications are the initial treatment of choice in chronic insomnia patients. These medications have a number of attributes that are particularly favorable for some patients with insomnia in some clinical settings including: rapid onset of effect, widespread availability in clinical practice, the absence of the need to institute a significant change in behavior, and effectiveness when behavioral targets are lacking. Further, some patients that are provided with information about the risks and benefits of the available therapies choose to pursue pharmacotherapy with hypnotic medications. While the long-standing reluctance to utilize these agents for chronic treatment might be a deterrent to initiating therapy with hypnotic medications in those with particularly long-lasting insomnia, the available research data suggest that the risk-benefit ratio for at least some hypnotic agents is more favorable than has been assumed. These data suggest that, for several agents, chronic therapy for up to a year can be effective if needed in patients with chronic insomnia. Lastly, it is important to bear in mind that it may be useful to administer hypnotics as initial therapy in combination with CBT. When administered together, patients may benefit from the advantages that both have to offer and experience rapid and sustained relief of insomnia.

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