The long-term use of sedative hypnotics in chronic insomnia

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ABSTRACT

Symptoms of insomnia are highly prevalent among adults and insomnia is often a chronic condition which may occur for years. Sedative hypnotics including benzodiazepines (BZDs), zolpidem, eszopiclone, and zaleplon (NBZDs) are commonly used to treat insomnia. The longest controlled studies evaluating the safety and efficacy of NBZDs were 12 months in duration and 2 months in duration for the BZD, temazepam. These studies suggest that NBZDs continue to be effective and safe when used for up to 12 months. The short-term adverse effects are more common and more severe for BZDs than for NBZDs. Despite the current practice of using sedative hypnotics for longer durations, studies have yet to evaluate the long-term adverse effect profile.

KEYWORDS

sedative, hypnotic, insomnia, long-term use

INTRODUCTION AND BACKGROUND

Insomnia is defined as difficulty with sleep initiation, duration, quality or consolidation, which results in impairment of daytime functioning.[1] Symptoms of insomnia occur in 33% to 50% of adults, while insomnia causing distress or impairment occurs in 10% to 15% of adults. Fifty to 75% of those with a psychiatric disorder or chronic pain have insomnia. Insomnia is often a chronic condition, as 70% of patients have insomnia at 1 year after baseline assessment and 50% have insomnia after 3 years according to long-term studies.[2] Chronic insomnia is defined as insomnia present for at least 1 month; whereas acute or transient insomnia lasts days to weeks.[1]

The American Academy of Sleep Medicine's (AASM) Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults recommends providing short-term pharmacologic therapy with sedative hypnotics along with behavioral and cognitive therapy to treat insomnia.[1] The specific hypnotics recommended are zolpidem, eszopiclone, zaleplon, and temazepam. Patients should be evaluated for the continued need of a sedative hypnotic 2 to 4 weeks after initiation. The guidelines suggest that the lowest effective dose should be used and the medication should be tapered and discontinued when possible. The long-term use of sedative hypnotics may be necessary in those with severe insomnia, refractory insomnia, and/or a chronic comorbid psychiatric disorder, substance use disorder, or medical condition. Patients using sedative hypnotics for longer than one month should have regular follow-up visits at least every 6 months to assess for efficacy, side effects, tolerance, and abuse or misuse of sedative hypnotics.

Several benzodiazepine receptor agonists are FDA approved and have demonstrated short-term efficacy for insomnia.[1,3] The BZDs include estazolam, temazepam, triazolam, quazepam, and flurazepam and the NBZDs include zaleplon, zolpidem, and eszopiclone. The AASM does not recommend a specific sedative hypnotic over another; however, triazolam is not recommended as a first-line agent as it may cause rebound insomnia. Likewise, flurazepam has a long half-life, which limits its use. The AASM's guideline indicates that the evidence for the long-term treatment of insomnia is limited to common clinical practice and expert opinion.

Guidelines from the National Institute of Health published in 1983 suggest medication use in the treatment of insomnia be limited to periods of several weeks as placebo-controlled trials at that time were limited to several weeks.[4] The short-term use of sedative hypnotics continues to be emphasized despite insomnia's often chronic presentation. The definition of chronic varies in clinical studies from 30 days to 6 months. However, insomnia persisting for a year or longer may continue for a decade or more.[5] Therefore when considering the long-term use of sedative hypnotics, "long-term" could refer to use for months to years or even decades. Studies of the safety and efficacy of the long-term use of sedative hypnotics are thus far limited to only 12 months.

LITERATURE EVIDENCE

Nightly administration of zolpidem for insomnia has been studied in 12-month, 8-month, and 3-month, randomized, double-blind, placebo-controlled studies.[6-8] Additionally, intermittent use of zolpidem was studied in a 6-month, randomized, double-blind, placebo-controlled study.[9] The

results of these studies indicate that the long-term use of zolpidem for 3 to 12 months maintains efficacy for sleep improvement and is not associated with tolerance or rebound insomnia.[6-9] The most common side effects reported in the studies were headaches, drowsiness, and dizziness.

Eszopiclone has been studied for up to 12 months for insomnia.[12] In randomized, double-blind, placebo-controlled studies of 3 months and 6 months of nightly administration of eszopiclone, efficacy was maintained with no evidence of tolerance or rebound insomnia.[10-11] The 6-month study was completed in patients aged 65 to 85 years. Eszopiclone was also studied in a 12-month, open-label, extension study of the aforementioned 3-month study.[12] This study found sustained efficacy and no evidence of tolerance. However, the sleep quality upon discontinuation was not evaluated. Walsh, et al, conducted a 6-month, randomized, double-blind, placebo-controlled study of eszopiclone which found improvement in quality of life, reduced work limitations, and reduced global insomnia severity.[13] No tolerance or discontinuation effects were found.

Zaleplon was studied in an open-label, 12-month extension of a 14-day study.[14] The average age of patients was 73 years. The study found improvement in sleep without tolerance or rebound insomnia. The most common adverse effects were headache, infection, backache, rhinitis, and dizziness.

The results of the long-term studies of the NBZDs indicate that these sedative hypnotics are safe and effective when used for up to 12 months.[7,12,14] Additionally, these sedative hypnotics do not appear to be associated with tolerance or rebound insomnia. Although BZDs are much older medications than NBZDs, there remains little evidence for their long-term use. For example temazepam has been studied in a 2-month placebo-controlled study and tolerance and rebound insomnia were not evaluated.[15]

In general, adverse effects are usually less common and less severe for the NBZDs than for the BZDs.[4] Short-term adverse effects of BZDs include next-day sedation, psychomotor impairment, and cognitive impairment, anterograde amnesia, and respiratory depression.[16-18] Benzodiazepines are associated with tolerance, rebound insomnia, and withdrawal at discontinuation. For the NBZDs, in comparison, respiratory depression has not been reported, tolerance and withdrawal are unlikely, rebound insomnia is rare, and the NBZDs have limited effects on daytime performance, memory and psychomotor tasks.[16-18] Furthermore, the NBZDs have a decreased likelihood of causing next-day sedation compared to the BZDs.[18] The most common side effects reported in short-term studies of the NBZDs are not serious and include headaches, nausea, diarrhea, dizziness, and somnolence.[17] However, more serious side effects have been reported with zolpidem including sleepwalking, telephone conversations, hallucinations, house cleaning, sleep driving, and sleep walking.[16,19]

Although insomnia and the use of sedative hypnotics are independently associated with falls in the elderly, a review of the literature by Allain, et al. concludes that sedative hypnotics (BZDs and NBZDs) increase the risk for postural instability, falls, and hip fractures in the elderly with most of the events occurring during the time of BZD use.[2,20] Additionally, a prospective, population-based study conducted in 1063 elderly adults (average age 78 years) found that in a 15-year follow-up period the new use of BZDs was associated with an increased risk of dementia (Hazard Ratio 1.6, 95% Confidence Interval of 1.08 to 2.38).[21]

In comparison, the NBZDs are newer and their long-term use has not been as extensively studied.[4,16,17] Zolpidem is the oldest of the NBZDs and post-marketing surveillance indicated that the most common long-term adverse effects were similar to those experienced in the short-term (nausea, diarrhea, headaches, dizziness, hallucinations, and residual daytime sedation).[17] A serious side effect experienced in one case was paranoid symptoms. Confusion, disorientation, obsessive ideas, delirium and psychosis were reported at an incidence of 1%. It was also noted that, in some cases, zolpidem use might have contributed to hepatic toxicity and worsening hepatic encephalopathy. Collectively, there is minimal long-term safety information available for the NBZDs and further research is needed in this area to fully characterize the long-term effects.[4,16,17]

Concern remains regarding the effects of sedative hypnotics on road traffic accidents. Studies have found that road accidents are higher among patients using BZDs compared to those who are not using BZDs.[4] An epidemiological, within-person, case-crossover study evaluated the association between psychoactive drugs and road traffic accidents.[22] Of 19,386 drivers involved in road traffic accidents, 1,789 were using a psychoactive drug, and 235 of those were using BZDs or zopiclone. The use of BZDs and zopiclone was associated with an increased risk of road traffic accidents (In-patient Exposure Odds Ratio: 1.62, 95% Confidence Interval 1.24 to 2.12). The authors noted that the anxiolytic BZDs were

associated with most of the risks for traffic accidents compared to the hypnotic BZDs. To further analyze the effect of BZDs on road traffic accidents, a systematic review was conducted.[22] The results of the individual studies were not combined into a composite outcome and some of the individual study results were conflicting. However, the authors concluded that exposure to BZDs is associated with an increased risk of road traffic accidents and the risk is higher within the first weeks after starting a BZD, after increasing the dose, and for BZDs with a long half-life.

In comparison, there is limited evidence regarding the effects of NBZDs on driving.[4] In January 2013, the FDA recommended manufacturers change the dosing recommendations on the label for zolpidem formulations due to the risk of early morning impairment in activities requiring alertness such as driving.[23] These recommendations are the result of adverse event reports and additional data submitted to the FDA which included further evaluation of zolpidem blood levels that may impair driving abilities. From these data it was determined that women eliminate zolpidem more slowly than men and are, therefore, more susceptible to next-morning impairments. Specifically, the FDA recommended manufacturers reduce the initial dose for the immediate release formulations (oral tablet, sublingual tablet, oral spray) for women from 10 mg nightly to 5 mg nightly and reduce the initial dose for the controlled release formulation for women from 12.5 mg to 6.25 mg nightly. The FDA also recommends health care professionals consider prescribing these lower doses in men.

In addition to the short and long-term effects previously described, there is also a concern for misuse and abuse as all of the sedative hypnotics are classified as controlled substances. Benzodiazepines have been more definitively associated with abuse potential than the NBZDs.[17,18] Nonetheless, abuse has been reported with the NBZDs and in many cases patients had a history of drug or alcohol dependence.[18,19] The long-term use of BZDs has been associated with physiological dependence.[16,18] It remains unclear whether the long-term use of sedative hypnotics increases the risk for misuse and abuse as compared with short-term use.

CONCLUSIONS

According to the British Association for Psychopharmacology 2010 Consensus Statement, tolerance to sedative hypnotics and dose escalation are uncommon, as many patients will use the same dose of sedative hypnotics for years.[4] Many patients will develop a psychological dependence and are not willing to stop using the sedative hypnotics. The safety and efficacy of BZDs for insomnia when used for greater than 2 months has not been evaluated. Studies suggest that the NBZDs remain effective for insomnia and are not associated with tolerance and discontinuation effects when used for up to 12 months, though patients with chronic insomnia may use sedative hypnotics for much longer time periods for which safety and efficacy has not been evaluated.

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How to cite this article
Heesch CB. The long-term use of sedative hypnotics in chronic insomnia. Ment Health Clin [Internet]. 2014;4(2):78-81. Available from: http://dx.doi.org/10.9740/mhc.n190097