Hypnotics in Insomnia: The Experience of Zolpidem

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ABSTRACT

Purpose: One of the most commonly prescribed medications to treat insomnia is zolpidem, a non-benzodiazepine compound that is available as an immediate-release oral tablet formulation, an extended-release oral formulation, an oral spray formulation, and as sublingual formulations. The purpose of this review was to summarize the data currently available on the efficacy and safety of zolpidem in the treatment of insomnia among adults.

Methods: Published studies on the use of zolpidem in the treatment of insomnia were identified by using combinations of relevant search terms in PubMed and Google Scholar. Studies were included if they were placebo- or active comparator–controlled studies, with the exception of trials on the long-term use of zolpidem. Studies were limited to those conducted in adults. Studies were not included if the patient population was small, if the study was not designed or powered to assess the efficacy or safety of zolpidem, if insomniac patients had a medical condition in addition to insomnia (with the exception of comorbid depression or anxiety for studies on comorbid insomnia), or if zolpidem was given concomitantly with any other therapy (with the exception of selective serotonin reuptake inhibitors for studies on comorbid insomnia).

Findings: Twenty-five studies designed to evaluate the efficacy of zolpidem in insomnia and 51 studies reporting the safety of zolpidem in insomnia were included in this review.

Implications: The studies discussed in this review report the efficacy and safety of zolpidem in both young adults and the elderly. It can be used for either bedtime or middle-of-the-night administration, over the short or long term, with minimal risk of withdrawal or abuse. The use of zolpidem is associated with rebound insomnia, complex sleep-related behaviors, and next-day residual effects (after middle-of-the-night dosing) on driving ability, memory, and psychomotor performance. (*Clin Ther*. 2014;36:1676–1701)

Key Words: chronic insomnia, primary insomnia, secondary insomnia, zolpidem.

INTRODUCTION

The central features of insomnia, as identified in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, are dissatisfaction with sleep quantity or quality accompanied by complaints of difficulty initiating or maintaining sleep that result in clinically significant distress or impairment in social, occupational, or other important areas of functioning.[1] Insomnia may occur during the course of another medical condition or mental disorder (comorbid insomnia), or it may occur independently (primary insomnia).[2] The standard approach to treating comorbid insomnia used to be to treat the primary disorder, and the resolution of insomnia was expected to follow once the primary disorder achieved remission.[3] In recent years, there has been a shift in the approach to treating comorbid insomnia. Comorbid insomnia is increasingly recognized as a separate disorder that requires treatment either on its own or in conjunction with the primary condition.[4]

Improving quantitative and qualitative aspects of sleep, improving daytime function, and reducing the distress and anxiety associated with poor sleep are the

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main goals of treatment.[5] Current treatment options for insomnia can be broadly categorized into nonpharmacologic and pharmacologic approaches. Nonpharmacologic treatment options include cognitive-behavioral therapy, which involves various behavioral interventions (eg, stimulus control therapy, relaxation training, sleep restriction therapy, sleep hygiene, paradoxical intention therapy).[6–11] Pharmacologic treatment options, indicated or off-label, include benzodiazepine receptor agonists, melatonin receptor agonists, sedating antidepressants, atypical antipsychotics, sedating antihistamines, and unregulated substances (eg, valerian, melatonin).[12–16] Patients also try self-help strategies including reading and relaxation, home remedies such as alcohol, and herbal therapies.[17]

One of the most commonly prescribed medications to treat insomnia is zolpidem, a nonbenzodiazepine compound that acts by modulating the binding of γ-aminobutyric acid (GABA) at the benzodiazepine-binding site on the $GABA_A$ receptor complex.[18] In 1992, the immediate-release oral tablet formulation of zolpidem was approved in the United States for the treatment of patients with insomnia.[19] In 2005, an extended-release formulation was approved for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[20,21] In 2008, an oral spray formulation of zolpidem was approved for the treatment of insomnia characterized by difficulty with sleep initiation.[22] More recently, sublingual formulations of zolpidem have been approved, one a sublingual tablet approved for bedtime administration, and the other a sublingual lozenge specifically approved for middle-of-the-night (MOTN) awakening and difficulty returning to sleep.[19,23–25]

The present review details the evidence supporting zolpidem as a current therapy for the treatment of insomnia, with a focus on its efficacy in treating sleep onset and maintenance; primary, comorbid, and chronic insomnia; and its benefits with regard to next-day residual effects, long-term use, "as-needed" use, and risk of abuse.

MATERIALS AND METHODS

Published studies on the use of zolpidem in the treatment of insomnia were identified by using PubMed and Google Scholar. Searches were conducted for articles that contained combinations of the following terms: *abuse, adverse events, as needed, chronic, comorbid, complex behaviors, dependence, efficacy, elderly, gender, guidelines, induction, insomnia, intermittent, latency, long-term, maintenance, middle-of-the-night, next-day, onset, parasomnia, pregnancy, primary, rebound, residual, safety, secondary, side effects, sleep, withdrawal*, and *zolpidem*. The literature search was limited to English language, with no restrictions regarding year of publication. Studies were included in this review if they were placebo- or active comparator–controlled trials, with the exception of studies on the long-term use of zolpidem that typically followed up patients taking zolpidem over extended periods and thus did not have a placebo or active comparator group. Studies were limited to those conducted in adults. Studies were not included if the patient population was small, if the study was not designed or powered to assess the efficacy or safety of zolpidem, if insomniac patients had a medical condition in addition to insomnia (with the exception of comorbid depression or anxiety for studies on comorbid insomnia), or if zolpidem was given concomitantly with any other therapy (with the exception of selective serotonin reuptake inhibitors for studies on comorbid insomnia). Studies supporting the efficacy of zolpidem that are discussed in detail in this review are listed in the Table.

EFFICACY OF ZOLPIDEM

Zolpidem in Primary Insomnia

Zolpidem is effective in treating primary insomnia in adults by improving the induction, maintenance, and duration of sleep (Table). In one study designed to subjectively evaluate the efficacy and safety of a nightly dose of zolpidem 10 mg in patients with primary insomnia, patients receiving zolpidem reported significantly longer total sleep time (422.2 [11.0] vs 389.0 [10.1] minutes, respectively; $P = 0.054$), fewer awakenings after sleep onset (0.8 [0.1] vs 1.2 [0.1]; $P = 0.014$), shorter time spent awake after sleep onset (18.1 [3.4] vs 34.6 [4.8] minutes; $P = 0.001$), shorter sleep latency (43.2 [6.9] vs 64.0 [7.7] minutes; $P = 0.001$), greater ease of falling asleep (34.8 [2.2] vs 45.2 [2.3]; $P = 0.004$; measured on a Visual Analog Scale where 0 = very easy and 100 = not at all easy), and better quality of sleep (2.2 [0.1] vs 2.5 [0.01]; $P = 0.007$; measured on a Likert Scale where 1 = excellent and 4 = poor) compared with patients receiving placebo.[26] Similarly, the efficacy of