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NIH INSOMNIA ABSTRACT

Efficacy of Benzodiazepine Receptor Agonists in the Treatment of Chronic Insomnia

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Eight benzodiazepine receptor agonists (BzRAs) are currently approved for the treatment of insomnia by the U.S. Food and Drug Administration. The term BzRA is derived from the recognized site of action of these drugs, which involves occupation of benzodiazepine receptors on the gamma-aminobutyric acid, type A (GABAA) receptor complex and facilitation of gamma-aminobutyric acid inhibition.

The appropriate medical use of hypnotics for insomnia is currently controversial. The National Institutes of Health guidelines from 1983[1] have been labeled as no longer current for medical practice. The majority of authors recommend BzRAs for short-term use, either for acute or chronic forms of insomnia. Some experts advocate nightly, long-term use of BzRAs in certain situations; others recommend intermittent use of BzRAs for chronic insomniacs.

Hypnotic efficacy variables have predominantly been measures of sleep induction, maintenance, and quality. Sleep induction and maintenance are measured with polysomnographic (PSG) recordings and/or patient reports. Sleep latency (whether PSG or self-report) is the standard sleep induction variable, and the number of awakenings and wake after sleep onset are the most common sleep maintenance measures. Total sleep time and sleep efficiency reflect both sleep induction and sleep maintenance properties. Sleep quality does not have an established PSG metric, but a variety of patient-reported or investigator-rated measures relate to the sleep quality construct.

Many studies have documented the hypnotic efficacy of BzRAs using patient reports, PSG, or both. Meta-analyses found medium to large effect sizes when comparing BzRAs to placebo on the following efficacy measures for chronic insomniacs: total sleep time (0.71–0.84), sleep latency (0.45–0.56), wake after sleep onset (0.89), number of awakenings (0.65–0.97), and sleep quality (0.62–1.20).[2,3] However, these meta-analyses have limitations because they combine data from multiple drugs at multiple doses with widely different pharmacokinetics, all of which may impact the outcome variables examined in the meta-analyses.

At the currently recommended doses, all of the BzRA hypnotics reduce sleep latency and most increase total sleep time. An exception is zaleplon, which does not reliably increase total sleep time. Specific sleep maintenance variables, as distinct from total sleep time, have not been commonly reported efficacy variables until recently.

A large number of studies document that the efficacy of BzRAs is present on the first night of administration in both acute and chronic insomnia. A large majority of hypnotic studies have been conducted with primary insomnia, but the available evidence suggests that they show similar effects in secondary insomnias.[4,5] No studies of ethnic, racial, or gender differences have been published.

Despite what is often stated, tolerance to the hypnotic effects of BzRAs does not develop in most well-designed studies. In rigorous polysomnographic studies, zolpidem (10 mg) and zaleplon (10 mg) have been shown to retain efficacy for 5 weeks of nightly use.[6,7] Unpublished investigations of estazolam (2 mg) and triazolam (0.25 mg) found sustained efficacy for 10–12 weeks of nightly use. A recent landmark study[8] of several hundred primary insomniacs found continued hypnotic efficacy of eszopiclone (3 mg) for 6 months of nightly use based on weekly self-reports of sleep latency, total sleep time, number of awakenings, sleep quality, and wake time after sleep onset. Nonblinded treatment with eszopiclone was continued for an additional 6 months without evidence of tolerance. Other recent studies also suggest that BzRAs maintain efficacy for treatment of insomnia for several months or more of nightly use.[9] Non-nightly use of zolpidem (10 mg) has been investigated for up to 12 weeks.[10] Ratings of sleep latency, total sleep time, number of awakenings, and sleep quality were all improved on nights with zolpidem. Additionally, investigator global ratings, which considered both medication nights and nonmedication nights, indicated reduced insomnia severity with zolpidem.

Controlled hypnotic effectiveness trials, per se, have not been carried out. However, some reports provide information which may approximate that of investigations of effectiveness. An epidemiologic study[11] found that of 532 patients chronically using hypnotics, 67 percent rated their sleep quality as improved "a lot" and only 14.4 percent reported little or no improvement. An interview study of individuals who had taken a medication to help them sleep in the past year found very high satisfaction rates.[12] Specifically, 84 percent of those taking triazolam, 82 percent taking flurazepam, 74 percent taking temazepam, and 61 percent taking over-the-counter aids reported they would take the medication for the same purpose in the future. Long-term, open-label studies also provide some information about effectiveness.[13,14] Zolpidem and zaleplon have been evaluated over periods of 6–12 months.

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In general, patients and physicians report sustained benefits of the hypnotics for the duration of the studies, without adverse reactions unique to long-term use.

Most definitions of insomnia include some form of subjective daytime impairment consequent to the sleep disruption. Yet, very few studies have investigated change in the daytime impairment of insomnia patients. In the 6-month eszopiclone study of primary insomniacs, patient reports of daytime alertness, ability to function during the daytime, and physical sense of well-being were all significantly improved with treatment. The waking impact of other forms of chronic insomnia may differ from primary insomnia and may respond to treatment. For example, periodic limb movement disorder[15] and rheumatoid arthritis[16] patients with insomnia have been shown to have lower than optimal Multiple Sleep Latency Test scores, which improve significantly after 6 nights of treatment with triazolam.

Future research should focus on the effects of hypnotics on sleep in: (1) insomnia with comorbid illness as well as the status of the comorbid condition (independent from sleep); (2) specific populations (i.e., older adults, ethnic and racial groups, etc.); and (3) dimensions of waking life (e.g., quality of life, cognition, occupational performance, health care utilization).

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