The Safety Risk Associated with Z-Medications to Treat Insomnia in Substance Use Disorder Patients

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Abstract

Z-medications are commonly prescribed in clinical practices despite the safety concerns. Although these medications are considered safer than benzodiazepines, both act on GABA-A receptors as an allosteric modulator. In clinical practice, the risk profile for both medications is not any different, particularly in substance use disorder population. The safety risk is more alarming due to possible abuse, dependence and tolerance related issues in this population. Physicians should be careful while prescribing these medications and if indicated, its use should be limited over brief period of time and close patient monitoring is recommended.

Keywords: Benzodiazepine receptor agonist; Substance use disorder; Z-medications

Introduction

Benzodiazepine receptor agonist is divided in two categories:

a) Benzodiazepine hypnotics and

b) Non-benzodiazepine hypnotics.

The prescription of Z-medications which is non-benzodiazepine hypnotic is common in daily clinical practice, particularly among primary medical providers to treat patients with insomnia. This trend is less observed among psychiatrists, but does exist. While treating substance use disorder population the prescription of Z-medications should be strongly discouraged secondary to well documented safety risks. There is sufficient data available suggesting against the prescription of Z-medications to treat insomnia in substance abuse patients. Though treating insomnia is essential in substance use disorder patients to prevent relapse on alcohol/drugs, be mindful of risk associated with hypnotics particularly with BZRA (Benzodiazepines and Non benzodiazepines hypnotics).

Classification of Z-medications

Name of medication Half-life (hr) Adult dose (mg).

Zaleplon   1   5-20
Zolpidem  1.5-4.5  5-10
Zolpidem CR  1.5-4.5 6.25-12.5
Eszopiclone  5-8  1-3

Eszopiclone is the only agent FDA approved to treat insomnia >30 day use in general population.

Insomnia symptoms indications

Zaleplon treats sleep onset.
Zolpidem IR treats sleep onset, Zolpidem Er treats sleep onset and maintenance, Eszopiclone treats sleep onset and maintenance.

BZRA-Non benzodiazepines are DEA IV schedule and pregnancy category C.

Mechanism of action

Sleep promoting neurotransmitter is GABA; Gamma amino butyric acid is a predominately inhibitory neurotransmitter in brain receptor (ventralateral preoptic nucleus). GABA Receptors: GABA-A, GABA-B, GABA-C. GABA-A receptor complex: Pantameric transmembrane structure, modulates chloride ion channel, and hyperpolarizes neurons. BZRA cause allosteric modification of the GABA-A receptor to potentiate GABA effect. (BZRA) Benzodiazepines hypnuptics (Non selective) bind with Bz α1, Bz α2 and Bz α3 subunits of GABA-A receptors. Bz α1: hypnotic and amnestic Bz α2 and Bz α3: antiseizure, and muscle relaxing. (BZRA) Non-benzodiazepines hypnuptics (Selective) bind mainly with Bzα1subunits of GABA-A receptor. Bz α1: hypnotic and amnestic Z-medications modify GABA-A receptor increase affinity/ effectiveness of GABA (Chloride channel), has similar efficacy to...
benzodiazepines, decrease sleep latency, and increase total sleep time. There is no clear change in sleep architecture/sleep staging.

Data suggesting safety risk profile while prescribing Z-medications

In a large cohort of patients attending United Kingdom prime care, anxioleptics and hypnotics drugs were associated with significant mortality over seven years period, after adjusting for a range of potential confounders. The dose response association with mortality, found for all the three classes of study drugs. (Benzodiazepines, Z-medications (Zaleplon, Zolpidem, Zopiclone) [1]. The fatal toxicity of Zopiclone was not significantly different from that of Benzodiazepines as a group when adjusted for usage [2].

While prescribing Zolpidem it’s recommended lower doses for women due to slower metabolism and possible excessive blood levels the following morning. It can cause impairment in driving skills, memory, and coordination. They have profound effect on nocturnal and next day psychomotor body balance, reaction times and ability to multitask. There is an overwhelming degree of evidence, both experimental and epidemiological, implicating benzodiazepines in particular, but Z-medications as well, with fatal and non-fatal motor vehicle accidents. Though some limitations and discrepancies persist, both streams of evidence (experimental and epidemiological), when considered together, support a strong causal argument for exposure of these drugs resulting in motor vehicle accidents. It seems more research is necessary to elucidate with certainty which medications, at what doses, and in which patients increases risk beyond an acceptable degree so as to enable effective targeted interventions to reduce motor vehicle harm [3]. Z-medications induced neuropsychiatric effects such as hallucinations and psychosis have been described for over 15 years particularly with Zolpidem. The mechanism doesn’t appear to be entirely dose related or due to elevated plasma concentration of Zolpidem [4]. Drug interaction between Zolpidem and various serotonergic and nor adrenergic agents include SSRI’s venlafaxine, and tricyclic antidepressants have been reported to induce hallucinations [5].

Tolerance, dependence, withdrawals are all reported with Z-medications though this appear to be less severe and with lower incidence than for traditional benzodiazepines in the treatment of insomnia [6]. Withdrawals symptomology resembles that from benzodiazepines, including insomnia, delirium, craving, anxiety, tremor, palpitations and rarely seizures and psychosis [7]. Rebound insomnia, upon immediate cessation of the hypnotic drug has been reported with higher dose of Zolpidem [8]. This phenomenon has not been reported with therapeutic doses of Zopiclone and Zaleplon [9]. The potential for Zolpidem abuse and dependence in insomniacs is being increasingly recognized with warning on product labels appearing since 2004 [10]. Though the abuse potential exists for all Z-medications it is more commonly reported for Zolpidem and Zopiclone [8,11].

Overdose, chronic abuse, poising and death have been reported from all Z-medications. In an American poison control center study, Zolpidem overdose was more likely to lead to intensive care admission when co ingested with over the counter cold and flu preparations, other psychotropic medication or ethanol [12]. Garnier et al reported the first large case series of Zolpidem poisoning in 1994, where toxicity predominately involved sedation with ingestion up to 1.4g [13]. Rarely did Zolpidem cause coma, respiratory depression, depression, cardiovascular toxicity or death. The reports of agitation, hallucinations, psychosis and coma from Z-medications overdose have been published [14]. Over the last few year’s increasingly flags from forensics cases, drug facilitated crimes and motor vehicle crash statistics indicate that mortality from Z-medications may be similar to benzodiazepines. Bizarre behaviors, falls, accidents, and other injuries may lead to death. The majority of cases in which Zolpidem was thought to contribute to death were overdoses with most common co-ingestants being alcohol, antidepressants, benzodiazepines and opioids [15]. A significant association between using Zolpidem and suicide or suicidal attempt in people with or without comorbid psychiatric issues [16].

Z-medications are potential risk of complex sleep related behavior such as sleep eating and sleep driving. However, risks of complex sleep-related behaviors and next-morning impairment have been increasingly recognized, and non-benzodiazepines should not be considered any safer than other hypnotics per se. One study found that Zolpidem accounted for 12 percent of all emergency department visits for adverse drug events related to psychiatric medication in the United States over the period of 2009 to 2011, and 21 percent of all such visits involving adult’s ≥65 years of age [17]. Perhaps surprisingly, Zolpidem was implicated in more Adult Emergency room visits than any other psychiatric medication and caused a markedly high number of Adult Emergency room visits relative to the number of outpatient visits at which it was prescribed, particularly compared with antidepressants and benzodiazepines [18].

The use of sedative-hypnotics in patients either with or without insomnia was associated with subsequent cancer development in the Taiwanese population. Increased risks of oral, liver, and breast cancer were found in the patients with the use of sedative-hypnotics. The use of sedative-hypnotics should be discouraged for treating patients with or without insomnia in Taiwan [19].

Improvements in sleep with sedative use are statistically significant, but the magnitude of effect is small. The increased risk of adverse events is statistically significant and potentially clinically relevant in older people at risk of falls and cognitive impairment. In people over 60, the benefits of these drugs may not justify the increased risk, particularly if the patient has additional risk factors for cognitive or psychomotor adverse events [20]. There is improved risk profile includes: the effects of Zaleplon on psychomotor and cognitive performance; tolerance, withdrawal and rebound; respiratory depression; sleep architecture; and other treatment-emergent adverse effects [9]. In terms of evidence regarding any association of Z-medications specifically to dementia, the evidence is primarily restricted to a few sub-analyses in benzodiazepine studies previously alluded to, which suggest a similar risk of dementia as was seen with benzodiazepines. A single Taiwanese case-control study reported an increased risk of dementia with Zolpidem compared with for non-users, but other than this there appears to be a lack of studies solely on Z-medications and dementia with benzodiazepines excluded [21,22].

It is also concluded in literature that anxioleptics, sedatives, and hypnotics are associated with a limited increase in the risk of fractures. For most drugs a dose-response relationship was present, and drugs with a half-life >24 h tended to be associated with a higher risk of fractures than drugs with a shorter half-life. This point to a dose-
The effect of benzodiazepines and Z-medications on respiratory disease states is not yet perfectly clear due to the disparity of results between acute respiratory effects as measured in smaller experimental studies and longer term clinical outcomes in observational studies. Given that population based studies examining outcomes from exposure to these drugs have been predominantly case-control and retrospective cohort designs, prospective evidence, or even a meta-analysis of the available studies would be useful to persuade researchers and clinicians of any causal truth behind these associations. This is yet another example where findings from one discipline are not clearly in accord with those of another for these drugs and efforts should be made to reconcile this discrepant mistranslation in findings between pharmacology and epidemiology [24].

Conclusion

BZRA (Non benzodiazepines hypnotics) have a structure that is different from the benzodiazepines and includes more targeted action at specific GABA type A receptor. Z-medications, although considered safer in comparison to benzodiazepines, are not free of risks. Z-medications have increased likelihood of abuse, relapse, dependency, tolerance and potential for overdose when combined with alcohol or other substances. Similar to benzodiazepines there is a significant mortality risk associated with Z-medications, which should discourage the daily use of these medications especially in substance use disorder patients.

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Conflict of Interest

Authors have no conflict of interest.

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