'Z'-hypnotics versus benzodiazepines for the treatment of insomnia

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Z-hypnotics have been perceived to be better than benzodiazepines for the treatment of insomnia for many years. NICE guidance focuses on cost effectiveness and purchase prices as there is limited convincing evidence to distinguish between these agents. This review aims to compare Z-drugs and benzodiazepines as hypnotic agents in terms of their efficacy, safety, tolerability and abuse potential.

Insomnia is characterised by a disturbance of normal sleep patterns – either reduced time asleep, delay in onset[1] or early morning wakening. It is associated with: a reduced quality of life; mental health problems; substance abuse; impaired function and road traffic accidents; risk of subsequent depression and anxiety, and possibly cardiovascular disease, all of which affect the economic burden due to reduced productivity and work absences.[2] The mainstay of treatment is non-pharmacological,[3] after first excluding other causes, *eg* physical pain or substance misuse.[4] Non-drug approaches include adopting good 'sleep hygiene' and keeping a sleep diary to identify potential causative factors. Aromatherapy with lavender oil or herbal remedies, *eg* valerian, is widely used. However, its efficacy has not been proven and caution is advised. Non-pharmacological treatments improve symptoms in 70–80% of patients, with lasting effects.[3] Cognitive behavioural therapy (CBT) has been shown to be as effective as pharmacological treatments, however, combinations may be better. If non-pharmacological interventions fail or insomnia causes significant daytime dysfunction and distress then hypnotics may be used. Licensed treatments include benzodiazepines (nitrazepam, temazepam, diazepam, lorazepam etc.) and Z-drugs (zopiclone, zaleplon, zolpidem – see Box),[5] which are the most commonly used hypnotics. The Z-drugs are structurally different to benzodiazepines and were developed in an attempt to optimise the pharmacokinetic and pharmacodynamic properties of benzodiazepines, such as faster onset and rapid clearance to minimise or eliminate daytime sedation, in addition to removing abuse potential, dependence and withdrawal.[5,6] Current practice shows Z-drugs are prescribed more than benzodiazepines, because they are perceived as more effective and safer (particularly in elderly), producing less tolerance, addiction and dependence.[7]

Box Z-drugs

Zaleplon is a very short-acting pyrazolopyrimidine (elimination half-life of 1 hour) with no active metabolites, which limits its duration of action and use but significantly reduces hangover risk. Zaleplon is useful in treating insomnia characterised by trouble falling asleep or waking during the night.[6]

Zolpidem is an imidazopyridine and predominantly hypnotic due to its high affinity for alpha-1 subunits.[10]

Zopiclone is a cyclopyrrolone, the elimination half-life of zopiclone and its active metabolite is 3.5-6.5 hours.[5] It is predominantly hypnotic due to its efficacy at several alpha subunits.

Efficacy

Both benzodiazepines and Z-drugs work by potentiating GABA activity.[8] Benzodiazepines bind to GABA receptors at the alpha-1, 2, 3 and 5 subtypes.[2] They have been used as hypnotics since the 1960s and when compared with a placebo, produce a marked and clinically meaningful effect on sleep duration.[9] Moreover, they are less effective in reducing sleep latency. Z-drugs are GABA-A receptor agonists: zolpidem and zaleplon are effective sedatives as they bind selectively to the alpha-1 (hypnotic) subunit, and zopiclone exhibits a unique receptor interaction.[6]

A meta-analysis comparing zolpidem and benzodiazepines found for patients 65 years old and younger they were equally as effective as a placebo, but for patients older than 65 years both had an increased risk of adverse effects.[3,11] Zolpidem, particularly the modified-release preparation,[2] causes statistically significantly fewer awakenings, a greater ease of sleep onset and improved sleep time than temazapam.[5] Similarly, studies comparing hypnotic properties found zopiclone (a cyclopyrrolone) is equal to or superior than benzodiazepines.[12] Patients taking zopiclone reported better quality

and duration of sleep, less time taken to get to sleep, fewer awakenings and a greater ease of getting to sleep. These benefits (*ie* fewer adverse effects and rebound insomnia, less psychomotor impairment and much less residual impairment improving daytime functioning) outweigh the risks associated with zopiclone.

Tolerability

The beneficial effects (NNT=13) of using hypnotics for insomnia are small compared with their risks of causing harm (NNH=6).[13] Benzodiazepines have a larger receptor occupation than Z-drugs giving rise to profound pharmacodynamic actions.[6] Adverse effects of benzodiazepines include headache, blurred vision, gastrointestinal upset, confusion, ataxia and paradoxical reactions, which outweigh their potential clinical benefits.[4] In addition, many have long-acting active metabolites that accumulate when taken chronically.[14] As highlighted by the British Association for Psychopharmacology (BAP) consensus statement, the adverse effects of Z-drugs are comparable with benzodiazepines, however, a meta-analysis of randomised controlled trials of benzodiazepines and Z-drugs has shown adverse effects are less common and less severe for the Z-drugs zolpidem and zaleplon.[2] It looked at the most commonly reported adverse effects, which were more frequent for the benzodiazepines, and included somnolence, headache, dizziness, nausea and fatigue. Fatigue was not reported for the non-benzodiazepine group.

Benzodiazepine-induced drowsiness and cognitive impairment is particularly problematic in patients with pre-existing cognitive conditions, *eg* dementia. At typical doses Z-drugs do not cause as much cognitive impairment as benzodiazepines.[15] This is shown in studies using digit-symbol substitution tests and memory tests.[2] In addition, when studied, benzodiazepine use is associated with more reports of drowsiness, dizziness and cognitive impairment (reported as memory loss, confusion and disorientation). Zolpidem- and zopiclone-induced body balance impairment is a dose-dependent effect with more risk during the first few hours of administration. This is observed to a lesser extent with zaleplon due to its elimination half-life.[16]

Hangover effects of hypnotics are dose-dependent and vary depending on pharmacokinetics, *ie* duration of action, which is determined by elimination half-life (most likely if greater than six hours, *eg* diazepam and zopiclone due to residual drug in the brain), as well as individual susceptibility, *ie* rate of drug clearance.[2,13] The half-lives of the 'short- and intermediate-acting' benzodiazepines range from 6–17 hours so all have the potential to cause daytime problems; for example, lorazepam has a half-life of 10–20 hours, alprazolam 6–12 hours and temazepam 8–22 hours. Therapeutic doses of zopiclone have a high risk of psychomotor and cognitive impairment, poor mental alertness and poor motor coordination, within 12 hours of administration.[17] The risk of hangover effects with zopiclone is comparable or less than short-acting benzodiazepines. Zolpidem can, dose-dependently, impair word recall and recognition 6–8 hours post-administration after which the risk is reduced.[10] Zaleplon may cause significant, dose-independent psychomotor impairment immediately after administration, but not the next day,[12] or during the night.[13]

Both Z-drugs, especially zolpidem, and short-acting benzodiazepines such as triazolam, may cause complex behaviours such as sleep-walking, sleep-driving and hypnopompic hallucinations,[15] but this is unconfirmed by electroencephalography[13] and it is unclear as to whether this is more likely in predisposed patients.

Hypnotics and amnesia

All hypnotics have the ability to cause amnestic effects as they reduce sleep latency and block memory consolidation.[13] Benzodiazepine-induced anterograde amnesia may be due to changes in sleep architecture, particularly a profound decrease in REM sleep.[12] Z-drugs have the ability to cause amnesia at higher doses and within the first few hours of administration but not as much as benzodiazepines.[13]

Safety

Both benzodiazepines and Z-drugs may cause respiratory depression, however, the myorelaxant effect is 10–40 times greater in benzodiazepines.[12] Comorbid respiratory impairments such as COPD and obstructive sleep apnoea may be exacerbated by benzodiazepines.[12,18] Historically-used hypnotics, *eg* choral hydrate, chlormethiazole and barbiturates, have the potential to cause lethal respiratory depression in overdose due to their low therapeutic ratios, and their effects are very difficult to reverse so they are no longer recommended.[18]

Benzodiazepines potentiate CNS depression and impairment with other sedatives and alcohol.[11] However, CNS depression is not likely with Z-drugs unless they are taken with alcohol. There is also an increased risk of suicidal behaviour when

benzodiazepines are taken with alcohol but this is not seen with Z-drugs.[2]

Both benzodiazepines and Z-drugs (particularly zolpidem) can cause unpredictable paradoxical reactions, characterised by acute excitement, hyperactivity, vivid dreams, sexual disinhibition, and an increase in hostility, anxiety and aggression.[4,19,20] The risk of these reactions is increased with high-potency or short-acting drugs, in the young and old and in those with a learning disability, neurological disorder, CNS degenerative disease or a history of aggression.[4]

One major patient safety concern is impaired driving performance, which may be hypnotic-induced or sleep-deprivation-induced. Benzodiazepines, as well as zopiclone and zolpidem, increase the risk of road traffic accidents.[9] The risk is more than doubled in zopiclone and zolpidem users compared with unexposed drivers.[13] The European Medicines Agency[21] issued advice in 2014 regarding zolpidem; stating the recommended dose should be a single dose just before bed and, for at least eight hours following a dose, patients should not drive, or undertake activities needing alertness. It must not be taken with other CNS drugs, alcohol or illicit drugs as they significantly increase the risk of impairment.

The FDA[22] issued a similar announcement for extended-release zolpidem, as residual levels are high enough to cause impairment especially at higher doses. Zopiclone may also induce driving impairment the morning after or in the afternoon following a 15mg dose.[13] Whereas, next-day driving impairment is unlikely with zaleplon as long as at least four hours have passed after taking the drug and before driving, due to its very short half-life.[13] Moreover, long-acting benzodiazepines are more likely to cause next-day driving impairments than zolpidem, zopiclone, nitrazepam, and non-users of hyponotics, for example flunitrazepam has been associated with four times the risk of a road traffic collision.[13]

Use in the elderly

Benzodiazepines and Z-drugs are associated with similar risks in elderly patients. Older patients are likely to be prescribed hypnotics due to age-related changes in sleep patterns, and carry a special set of considerations. They tend to have a reduced renal and/or hepatic function, which can prolong drug metabolism, elimination and action. In addition, their receptors are more sensitive and even short-acting GABA-ergic drugs can compromise balance and decision making during the night.[1,13] This can impair mental or psychomotor function, increasing the risk of falls and injury, which leads to increased morbidity and consequent healthcare costs. There is at least a 50% increased risk of hip fractures when benzodiazepines are used in the elderly, especially during initial treatment and after continuous use (≥1 month).[4]

Abuse and tolerance

All hypnotics have abuse potential. The risk is increased with chronic use of shorter-acting hypnotics at higher doses, a history of substance dependency, personality disorders and no medical supervision.[5] Benzodiazepines can enhance or prolong 'drug-induced highs' and relieve withdrawal effects, *eg* alcohol withdrawal.[5] They are widely acknowledged to cause addiction and withdrawal. Chronic benzodiazepine use is associated with tolerance and dependence (but not in all patients). NICE[5] estimates that 10–30% of patients taking benzodiazepines chronically are physically dependent and at least a third experience problems on stopping or reducing the dose.[4]

Withdrawal syndrome has been reported after stopping all hypnotics, except zaleplon.[2] This includes transient worsening of insomnia, headaches or myalgia, confusion, and severe anxiety, restlessness, and irritability.[10,17] Short-acting benzodiazepines, *eg* lorazepam, are associated with the greatest risk of withdrawal.[4] These concerns restrict hypnotic use to severe insomnia for up to four weeks (maximum) at the lowest effective dose as per the then Committee on Safety of Medicines (CSM) cautionary statement.[23] Similarly, for Z-drugs the summary of product characteristics (SmPC) document that prolonged use may cause some loss

Novel therapy

Eszopiclone is the S-enantiomer of zopiclone developed for a more favorable pharmacokinetic and side effect profile. Its affinity for the alpha-1, 2, 3 and 5 receptor subtypes is similar to that of zopiclone, however, it is particularly efficacious at alpha-2 and 3 receptors, which can improve sleep induction, but much less efficacious at alpha-5 receptors reducing the ability to cause cognitive adverse effects.[24] It therefore has advantages in next-day functioning and alertness. Eszopiclone has shown to significantly improve sleep latency, total time asleep and reduce napping,[3] which is continued for a number of months. There is less tolerance, dependence and rebound insomnia on withdrawal. However, adverse effects include unpleasant taste, amnesia, hallucinations, worsening of depression and reports of euphoria in high doses.[11,24] The drug is available in the USA but no launch date has been set for Europe. The acquisition cost of eszopiclone in the US is slightly more than, but comparable to, the cost of immediate-release zolpidem and zaleplon but significantly less than modified-release zolpidem.[25]

of hypnotic effect and some dependence (the risk is increased with dose and duration) therefore duration is restricted to four weeks for zopiclone and zolpidem[10,17] and two weeks for zaleplon.[15] Despite acting on the same receptor the risk of tolerance, dependence and abuse with Z-drugs is different, due to differing pharmacology.[6] Most studies have shown little dependence with zopiclone or zaleplon and tolerance is unlikely with zopiclone because, on chronic use, it causes less receptor adaptation, which is owed to its distinctive thermodynamic interaction with the GABA receptor.[6] A study comparing abuse potential of zaleplon and triazolam, a very short-acting benzodiazepine, found zaleplon did not have abuse potential.[12]

Conclusions

Current perception that Z-drugs are safer than benzodiazepines is inaccurate; they tend to have a quicker onset and shorter duration of action but produce similar side-effects, so are not suitable substitutions. There is a variation between the different half-lives; hypnotics with the shorter half-lives tend to be safer producing less residual problems and adverse effects in most patients, but have higher risks of withdrawal so should only be used short-term. Benzodiazepines still carry the greatest risk of tolerance and abuse potential when compared with Z-drugs. Consideration of patient characteristics as well as pharmacokinetic differences between drugs before offering a hypnotic is vital. All hypnotics should be used short-term or intermittently and be reviewed regularly. This caution should be explained to patients along with information about the hypnotic prescribed to limit abuse potential.

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Declarations of interest

No conflicts of interest were declared. This was submitted as part of University of Aston Certificate in Psychiatric Therapeutics.

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