Current issues in the use of benzodiazepines for the treatment of insomnia

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ABSTRACT

Insomnia is the most common sleep-related complaint and the second most common overall complaint (after pain) reported in primary care settings. The benzodiazepines are still extensively used in the management of insomnia. Although short-term efficacy is established, long-term efficacy remains controversial, as relevant data are scanty and relapse, rebound and dependence on withdrawal not clearly distinguished. The advent of the newer non-benzodiazepine hypnotics have also led to an increased awareness of insomnia and treatment alternatives. This article reviews current evidence for the rational use of benzodiazepines.

Keywords:

Insomnia; Benzodiazepines;Dependence; Abuse

INTRODUCTION

Insomnia affects 35% of the general population during the course of a year, but despite its high prevalence, 69% of patients suffering from sleep disorders never report it to health care providers.[1] The benzodiazepines were first introduced over 30 years ago, and are the most frequently prescribed drugs for insomnia. They were originally marketed as improvements on the barbiturates and meprobamate.[2]

This group includes the classic benzodiazepine hypnotics and the newer non-benzodiazepines, zolpidem and zaleplon.

The benzodiazepine agonists have a common site of action on the gamma aminobutyric acid Type A receptor complex ($GABA_A$) that consists of a site for benzodiazepines and a chloride ion channel. The benzodiazepines and non-benzodiazepines are GABA synergists, since they have an allosteric augmenting effect on the GABA receptor.

GABA is an inhibitory transmitter substance, which opens chloride channels, so that chloride flows to the inside and hyperpolarizes the cell. As a result there is a reduction in the rate of secondary neuronal discharge, which then mediates a secondary non-selective inhibition of mono-adrenergic neuronal activity.[3]

Neuroscience has found evidence of 2 subtypes of central nervous system benzodiazepine receptors (BZ), also called omega receptors:-

BZ_1 (Omega 1) and BZ_2 (Omega 2)

BZ_1 receptors are believed to be involved in mediation of sleep.

BZ_2 receptors are believed to be involved in cognition, memory and motor control.[4]

Theoretically, a benzodiazepine agonist that binds to BZ_1 receptors has fewer adverse cognitive effects (e.g. zolpidem). The development of the non-benzodiazepine receptor agonists has led to the

hope of developing an even safer generation of benzodiazepine receptor agonists.[3]

The elimination half-lives of the sedative hypnotic agents varies widely. Adverse events such as memory impairment and excessive daytime somnolence tend to occur when active metabolites accumulate. Flurazepam and quazepam have the longest elimination half-lives (36 - 120hrs) and therefore has the advantage of providing next-day anxiolytic activity and lowering the likelihood of rebound insomnia. Agents with intermediate elimination half-lives (10 - 24hrs) and no active metabolites include temazepam and estazolam. Agents with very short elimination half-lives (2 - 5 hrs) include triazolam and zolpidem. (Less residual effects but higher withdrawal phenomenon).[5]

A meta-analysis of 89 randomised controlled trials comparing placebo to benzodiazepines found that benzodiazepines decrease sleep latency by 4.2 minutes (non significant) and significantly increased total sleep duration by 61-8 minutes. Patient reported (subjective) outcomes were more optimistic for sleep latency. Those randomised to benzodiazepine estimated a sleep latency decrease of 14.3%.[6] In one study, patients given a benzodiazepine overestimated their sleep duration by an average of 72 minutes as compared with EEG recordings . The benzodiazepine was then abruptly withdrawn, and patients slept poorly, but underestimated their duration of sleep by 1 hour. Thus, the symptomatic improvement on hypnotic and worsening on withdrawal are magnified in opposite directions by these subjective discrepancies.[2]

The hypnotic efficacy of the benzodiazepine and non-benzodiazepine agents is established in samples of primary insomniacs. Data supporting the efficacy of the non-benzodiazepine agonists in psychiatric insomniacs is less complete, but are suggestive of a beneficial effect.[7] The majority of studies reviewed were of a limited treatment duration (minimum 7 - days) and lacked follow-up data.

A strong placebo effect is observed in most studies comparing benzodiazepines to placebo in the treatment of insomnia. Placebo treated patients usually show steady reductions in sleep latency throughout clinical trials.[8] This may be explained as part of the spon-

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taneous waxing and waning of insomnia symptoms or perhaps a response to the behaviour constraints placed upon subjects as part of participation in a clinical trial. This strong placebo effect has an important implication: anecdotal reports and uncontrolled trials suggesting hypnotic efficacy for sedating anti-depressants could be explained as a placebo response.[7]

Hypnotic agents are primarily indicated for the short-term management of insomnia (< 4 weeks). Therapy beyond 4 weeks constitutes off-label use (according to the FDA). However, up to 15% of individuals who use hypnotics continue to take them longer than 1 year.[9]

RISKS OF USE OF BENZODIAZEPINES
Psychological
Paradoxical effects, although uncommon can present a major management problem. The patient may become more anxious and panicky. Abnormal effects may develop such as hostility or depression, antisocial behaviour may supervene with rare cases of violence to persons or property. The interaction with alcohol is particularly dangerous.[2]

Psychomotor effects
Benzodiazepines can impair psychomotor functions such as those involving speed and accuracy. Tasks requiring sustained attention and concentration can be markedly disrupted by administration of benzodiazepines. Effects are strongly dose related and vary from drug to drug. On repeated dosing, normal subjects show the well-known phenomena of tolerance, so that impairments wane over a week or so.[2]

Cognitive effects
In memory tasks, benzodiazepines disrupt the consolidation process in semantic (verbal) memory whereby material in short-term stores is transferred to long-term stores. Thus, and individual given a benzodiazepine can remember immediate information and that remembered before the benzodiazepine was administered, but may have difficulty recalling material given after taking the benzodiazepines (anterograde amnesia). Memory problems in the elderly taking benzodiazepines may lead to the misdiagnosis of Dementia.

Real life effects
Epidemiological data indicates that benzodiazepines contribute to road accidents and domestic accidents to a much lesser extent than alcohol. However, Canadian research has demonstrated a several-fold excess risk for hospitalisation for accidental injury after benzodiazepine use, particularly during the first two weeks of usage.[10]

Physical effects
These include vertigo, dizziness, dysarthria and ataxia. In the elderly, in co-ordination may lead to falls. Other adverse effects include rash, weight gain, impaired sexual function, menstrual irregularities and occasionally blood dyscrasias. Although some drug interactions do occur (e.g. cimetidine), they are not usually clinically significant. Potentiation of central nervous system depressants especially alcohol is the main problem.[2] Deliberate overdose is quite frequent but usually the patient recovers within 48 hours. However, benzodiazepines can be dangerous in the young, the old and the physically ill, particularly those with respiratory insufficiency.

DEPENDENCE AND ABUSE
Both the therapeutic and unwanted effects of the benzodiazepines show tolerance. This does not usually develop into full-blown tolerance with escalation of dose to several times the therapeutic levels as with some other drugs. Patients on such high doses are physically dependant and may suffer severe, even life threatening withdrawal reactions, including seizures or psychotic symptoms if the medication is stopped abruptly.

These patients also show drug-seeking behaviour, so they are psychologically dependant as well. It is now generally accepted that some, perhaps as many as 10 - 30% of long-term users, develop a state of physical dependence despite remaining on therapeutic doses.

Even after short courses of treatment, rebound - a marked worsening of symptom beyond pre-treatment levels - can follow discontinuation, but this can be minimised by tapering. This is most common after stopping short-acting compounds.

Withdrawal reactions may ensue after long-term use at therapeutic dosage, even after tapering. The symptoms are typical of withdrawal from sedative /hypnotic/alcohol group of drugs and include almost pathognomic perceptual symptoms such as photophobia, hyperacusis and feeling of incesscent movement. The symptoms come on within 48 hours of stopping a medium acting benzodiazepine such as lorazepam or temazepam and 5 - 10 days after stopping long acting drugs like diazepam. Symptoms usually disappear over a few weeks but occasionally patients complain of symptoms persisting for months. Withdrawal from lorazepam is more difficult to accomplish than from diazepam.

The whole topic of normal-dose dependence remains under debate, but there is general agreement that it is a relevant factor to consider when starting a patient on a benzodiazepine. It is difficult to predict who will progress to long-term use and become dependent, and how severe any subsequent withdrawal might be. The prognosis is not good, with less than half of long term users achieving sustained abstinence. Some patients become clinically depressed after withdrawal.

Benzodiazepines pose a major addiction problem worldwide. As part of polydrug abuse, benzodiazepines are used to intensify euphoria with opioids, as well as ease the "crash" down from stimulants like amphetamine and cocaine. Benzodiazepines are also used by themselves: taken by mouth, sniffed or sometimes intravenously. Worldwide flunitrazepam is believed to be the greatest problem, and its abuse occurs even in countries where it is not licensed.

The rational use of the benzodiazepine receptor agonists has been controversial for years. There appears to be virtually no evidence to support the chronic use of benzodiazepines in the management of insomnia. Further complications are the problems of relapse, rebound or withdrawl on discontinuation. Chronic use can be misread as continued efficacy, evidence that the benzodiazepines were merely acting to suppress symptoms of discontinuation.

Studying the long-term efficacy of the benzodiazepines is objectified because of the use of the polysomnograph. Fairly consistency, sleep, EEG measures of hypnotic effect reverts to pre-treatment values after 1 - 4 weeks. Despite this most patients claim that some benefit remains and may insist on continuing medication. This demonstrates the mismatch between subjective and objective measures.[2] Since the introduction of chlordiazepoxide 30 years ago, all pharmacological clinical trials in adult and geriatric patients have addressed only short term interventions (lasting several days to several weeks), and their immediate responses. There are no data from randomised clinical trials about the ability of interventions to produce sustained effects for more than 35 days. Questions remain unanswered about the long-term efficacy of medication in a disorder that is typically chronic and relapsing.

The non-benzodiazepine agents theoretically provide advantages above the benzodiazepine receptor agents, due to their relative selective stimulation of the BZ_1 receptor, thus eliminating the unwanted effects of the benzodiazepines. Their efficacy has been proven to be better than placebo in insomnia and at least as good as the benzodiazepines.

Zopiclone has often been thought of as a safer sedative, but a meta-analysis by Holbrook et al does not suggest any superiority of this agent.[6] Zolpidem and zaleplon are the newer non-benzodiazepines. They possess comparable hypnotic efficacy in diminishing sleep latency and they both have a rapid onset of action.

Zolpidem has a half life of 1.5 -3.2 hours. Due to its short half life, initial studies have indicated that bedtime administration of zolpidem is not associated with residual sedation or memory impairment when given at its recommended doses. Tolerance does not generally occur, but has been noted at very high doses. The development of dependence has been reported on extremely high doses. The use of zolpidem should be restricted to recommended doses of 5 to 10 mg.[9] Zaleplon is absorbed and eliminated in approximately 1 hour, possessing both a rapid onset of action and a short half life. The short half life also allows it to be administered in the middle of the night, on an as needed basis, for patients with sleep maintenance insomnia. The minimum safe period is 4 hours after administration.[11] Intermittent bedtime administration of the non-benzodiazepine, zolpidem has been shown to provide global improvement in daytime functioning.[7] Growing evidence supports the safety of middle of the night dosing of zaleplon.[7]

CONCLUSION

Pharmacological management of insomnia is continually evolving - Benzodiazepines and non-benzodiazepines have the best evidence for efficacy as hypnotics, although sedating antidepressants are popularly prescribed.

The introduction of the non-benzodiazepine receptor agonists provides an opportunity to understand different patterns of pharmacological activity with mechanistic differences in receptor activity. The impact of insomnia on daytime functioning and long-term health and socio-economic functioning has been recognised. Controlled studies are needed to determine the long-term efficacy of hypnotics in patients suffering from co-morbid psychiatric illness and insomnia. There is a clear need for further research in the area of non-pharmacological intervention.

From an evidence-based point of view, benzodiazepine hypnotics should only be tried after sleep hygiene and nonpharmacological measures have been considered. For physicians faced with the patient where other treatment have been exhausted and they feel they must prescribe a benzodiazepine, the drug should be discontinued within 2 - 4 weeks, because it is unlikely to remain effective in the long term.

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Commentary

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The article presents a clear concise summary of available information on the subject. The topic remains timely as insomnia continues to negatively affect the daily functioning of patients, diminishing the quality of their lives and in its' chronic form it is associated with (and in some situations can be regarded as a risk factor for) psychiatric (depression) and physical (cardiovascular) illness.

While current data provides reasonable support for the short-term use of benzodiazepines in insomnia, the usefulness of the data has limitations in that many questions remain unanswered: (1) Whilst almost all available studies are of short duration (Two weeks or less)[1], where do we find proof for the efficacy of longterm benzodiazepine use in insomnia? (2) When compared to placebo, what impact does benzodiazepine use have on overall quality of life and functional status? (3) Do the benefits of benzodiazepines for the treatment of insomnia counterbalance with the associated risks ie can the possibility of cognitive impairment or dependence be adequately weighed against any extra minutes of sleep gained? Answers to these and other issues can only be provided by longterm randomized, placebo-controlled, parallel group, double-blind trials.

Furthermore, the use of non-pharmacological alternatives for the treatment of insomnia i.e. comparisons between the efficacy of educational, health promotional or psychological interventions with benzodiazepines is an area where research remains much needed.

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