Insomnia in the elderly – Is an evidence-based approach possible?

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Introduction

Insomnia is both a frequent complaint that the elderly bring to the family practitioner and a source of discomfort to that practitioner. A commonly cited figure is that up to 42% of elderly patients (in this case in four American locations) report difficulty with falling asleep or staying asleep.[1] This survey also identified a number of risk factors for incident insomnia in this age group. These risk factors include chronic disease, depressed mood, physical disability, poor perceived health and widowhood. The authors concluded that "[b]ecause the vast majority of incident cases of insomnia were among persons with one or more of these risk factors, these data do not support a model of incident insomnia caused by the aging process per se".

There is no doubt that the vast majority of practitioners would be able to describe the features of the condition with accuracy, as well as describe an appropriate theoretical approach to its management. What is also certain is that many would be able to describe discordance between their own perceptions about the condition and its management and those of their patients, particularly the elderly. This is best summed up by a cross-sectional study conducted in Canada, in which questionnaires were given to 93 patients over the age of 60 years (all using benzodiazepines for insomnia) and 25 medical practitioners.[2] The main outcome was related to the perception of benefit and risk, scored on Likert scales of 1 (least) to 5 (most). The discordance noted by the authors was striking: patient perceptions of the benefits of benzodiazepines exceeded those of the medical practitioners (mean scores of 3.85 vs. 2.84, difference 1.00 (95% confidence interval 0.69-1.32), $p < 0.001$), but the reverse was shown in relation to perceived risk (mean scores of 2.21 vs. 3.63, difference 1.42 (95% CI 1.07-1.77), $p < 0.001$). In short, patients perceive hypnotics to be of greater benefit than risk, whereas medical practitioners hold the reverse to be true.

The full extent of the use of hypnotics by elderly patients in South Africa is not known. Two cross-sectional surveys using a standard set of medicines considered potentially inappropriate in the elderly have shown some differences between private and public sector settings. A small number (219) of a large sample (48 416) of elderly patients was shown to have a chronic approval for a long-acting benzodiazepine, which is clearly unacceptable.[3] Within this group, advanced age (75 years or older) was shown to be positively associated with the risk of receiving one of these agents (relative risk 1.518; 95% CI 1.164 to 1.981), but female sex was not (RR 1.182; 95% CI 0.901 to 1.551). General practitioners were more likely than specialists to be responsible for these prescriptions (RR 3.115; 95% CI 1.983 to 4.862). However, a total of 1 541 patients were prescribed any of the benzodiazepine group of drugs. Of these, more than half (54.4%) were receiving low doses (less than one defined daily dose (DDD) per day), but 210 (0.4% of the total sample) were receiving 1.5 DDD or more per day. This should be a concern, as each of these was a prescription approved for chronic, ongoing use. In contrast, a survey of repeat prescriptions for 6 410 public sector patients showed none receiving the longer-acting benzodiazepines (lorazepam, oxazepam and temazepam), which are considered potentially inappropriate.[4] However, neither survey should be seen as a reason for complacency, and the problem remains a challenge in family practice. The Canadian survey referred to above concluded that physicians' perceptions of the risks associated with benzodiazepines in the elderly were not only not shared by their patients, but were also "not supported by the literature for short-acting benzodiazepines".[2] It also pointed to the potential usefulness of newer, short-acting non-benzodiazepines, the so-called "Z-drugs" (zopiclone, zolpidem and zaleplon).

This review will try to demonstrate whether there is truly an evidence base for such contentions.

The therapeutic objectives

The choice of an appropriate therapeutic objective is complicated by the wide variety of presenting complaints. Insomnia can be seen as a symptom complex consisting of difficulty with falling asleep, or staying asleep, or the experience of non-refreshing sleep, in combination with some daytime sequel.[5] One potentially useful distinction is between transient insomnia (sleep problems that last days to weeks) and chronic insomnia (lasting months to years). Noting that chronic insomnia may stem from repeated bouts of transient insomnia, Roth and Roehrs suggest the

following goals for therapy of the transient condition:

- reversing the sleep disruption,
- thereby preventing the deterioration of daytime performance, and
- preventing the evolution to chronic insomnia.[5]

Chronic insomnia is a far more complex condition, not least because of the presence of considerable co-morbidities. For example, it is possible that insomnia and depression share a common pathology. The therapeutic objectives should therefore be similarly connected. However, what is clear is that any use of a hypnotic agent must seek to achieve the first two objectives listed above – it must reverse the sleep disruption, but not contribute to any limitation of daytime performance. In that regard, what is important is not just evidence of efficacy in relation to sleep, but evidence of safety in relation to daytime sedation. The ideal hypnotic has been described as one that "will have a rapid sedating effect that does not persist into the desired waking time, will not promote the development of tolerance and dependence, and will have specific pharmacodynamic activity that avoids the adverse effects from undesired receptor activity, and will have low toxicity if an excessive dose is ingested".[6]

Evidence of efficacy and safety

A three-step practical approach to the treatment of insomnia has been described: firstly, considering an underlying cause for the insomnia; secondly, applying non-pharmacological therapy; and, finally, choosing a safe and effective pharmacological agent.7 Thus, before considering the efficacy of pharmacological approaches, it is worth considering what evidence exists for non-pharmacological therapies.

Three recent Cochrane reviews can be of some assistance in this field. It has been pointed out that sleep hygiene manoeuvres, while having "considerable face validity", have not been extensively tested for efficacy.[7] These include avoiding large meals at night; avoiding caffeine, tobacco and alcohol; reducing evening fluid intake; reserving the bedroom for sleep and sex; keeping to a consistent wake-up time; limiting daytime napping; and avoiding light, temperature and noise extremes. The combining of these changes with challenges to the negative thoughts, attitudes and beliefs about sleep can be considered cognitive behavioural interventions. The Cochrane review of this modality found six trials of sufficient quality to warrant inclusion.[8] Cognitive behavioural therapy was found to be mildly effective, but the effects were not particularly durable. The effects were greatest in reducing night waking (i.e. in sleep maintenance insomnia, as opposed to sleep onset latency). Increased exercise has also been suggested as beneficial. Not surprisingly, evidence for the efficacy of this intervention in the elderly was generally lacking. The Cochrane review found only one applicable trial in 43 participants.[9] Though significant improvements in total sleep duration, sleep onset latency and global sleep quality scores could be demonstrated, confidence intervals were wide. It was therefore suggested that the findings be interpreted with due caution. The third, related Cochrane review looked at the efficacy of bright-

light therapy.[10] No trials were found that met the inclusion criteria for the review.

These reviews are instructive in another sense – they demonstrate the bewildering variety of measures of efficacy, including the time taken to fall asleep (sleep onset latency), the time spent awake after sleep onset (WASO), total time awake (TWT), total sleep duration, early morning wakening, sleep efficiency (the ratio of time asleep over time in bed), self-reports of sleep satisfaction, various validated sleep scoring systems and measures of daytime functioning and quality of life. Some of these are subjective, while others lend themselves to objective measurement in the sleep laboratory (for example, using polysomnography). There is as yet no validated sleep-specific quality of life questionnaire.

Benzodiazepines

A meta-analysis of the use of the most commonly chosen hypnotics, the benzodiazepines, was conducted by Holbrook et al.11 In this meta-analysis, data from 45 randomised controlled trials (RCTs), in which a benzodiazepine was compared with a placebo or an alternative active drug, were considered. These included a total of 2 672 participants, of which 47% were women. However, the variation in measures of efficacy meant that not all trials could be included in respect of each measure.

Sleep-record latency was tested in eight studies involving 159 subjects. The time taken to fall asleep was shown to be 4.2 minutes shorter (95% CI -0.7 to 9.2) in those given benzodiazepines compared with those receiving a placebo. It is worth noting that the confidence interval included zero – in other words, it could be stated that, 95 times out of 100, the difference would fall between 0.7 minutes longer and 9.2 minutes shorter.

In two studies (35 patients), sleep records of total sleep duration were compared. Those receiving benzodiazepines slept for an average of 61.8 minutes longer (95% CI 37.4-86.2) than those in the placebo groups.

Patients' estimates of sleep latency were the subject of eight studies (n = 539). Those given benzodiazepines took 14.3 minutes shorter (95% CI 10.6-18.0) to fall asleep than those given placebos. However, when only high quality studies were included, the effect was somewhat smaller, but still significant (11.7 minutes, 95% CI 7.6-15.8).

Patients' estimates of sleep duration were obtainable from eight studies (n = 566). Those given benzodiazepines reported sleeping an average of 48.4 minutes longer (95% CI 39.6-57.1) than those given the placebo.

Two issues deserve close attention in relation to these results. The first is that all of these trials were of short duration, lasting one to 14 days. The second is that the actual benzodiazepines used also varied, including very short-acting (e.g. triazolam) and very long-acting (e.g. flurazepam) examples. The biggest difference in the benzodiazepines, which correlates well with the potential to cause daytime sedation, is the elimination half-life. On this basis, benzodiazepines can be divided into four groups:[12]

- ultra-short acting (half-life <6 hours) – midazolam, triazolam
- short acting (half-life 6-12 hours) – brotizolam, loprazolam, loremeta-zolam, oxazepam, temazepam
- intermediate acting (half-life 12-24 hours) – alprazolam, bromazepam, lorazepam
- long acting (half-life >24 hours) –

chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, flunitrazepam, flurazepam, ketazolam, nitrazepam, prazepam

Elimination half-life can be expected to be extended in the elderly, making the selection of a short enough acting agent to avoid daytime effects even more important. While it would be tempting to advocate the use of the agent with the shortest possible half-life, this approach is complicated by experience with triazolam. In a crossover study, healthy young (mean age 30 years) and elderly (mean age 69 years) subjects were given single doses of a placebo 0.125mg and 0.25mg of triazolam and then assessed after 24 hours.[13] Triazolam was associated with a greater degree of sedation and greater impairment of psychomotor performance in the healthy elderly subjects. It was shown that the cause was higher plasma concentrations due to reduced clearance. Consequently, it was suggested that doses in the elderly be reduced by 50%. However, this agent has also been associated with reports of confusion, bizarre behaviour and amnesia.[14] Triazolam has subsequently been withdrawn from a number of markets, including in the United Kingdom.[7] There is also a relationship between half-life and the development of tolerance and dependence.[15] It has been noted that long half-life agents maintain their efficacy over prolonged periods when given nightly. Their withdrawal does not generally cause rebound insomnia, but they are associated with daytime sedation. Intermediate half-life agents show variable daytime carryover effects, rebound and tolerance. However, the rapidly eliminated agents are associated with relatively rapid development of tolerance, as well as rebound insomnia, while being almost entirely free of daytime effects. There are some variations – tolerance is intense with triazolam and slight with midazolam. Rebound insomnia is also intense with triazolam and variable with midazolam.

In the meta-analysis, data from eight studies (n = 889) were pooled for daytime drowsiness . Patients on benzodiazepines were more likely to report this adverse effect during the three to seven days therapy than those receiving the placebo (odds ratio 2.4, 95% CI 1.8-3.4). However, given the short duration of the included trials, it was not surprising that dropout rates were similar between the groups.

In summary, evidence for the efficacy of benzodiazepines in insomnia is surprisingly modest, given their widespread use. As expected, clinical trials show little evidence of adverse effects, as these are usually of short duration. However, the problems associated with long-term use of the benzodiazepines, especially by the elderly, are well documented,. Undesirable sequelae of such use include a higher risk of motor vehicle accidents, falls and fractures, and fatal poisonings, as well as the development of dependence.[7] The advice given is invariably the same: only use benzodiazepines after sleep hygiene and other non-pharmacological approaches have failed, and then only for two to four weeks.

The non-benzodiazepines – the Z-drugs

What has confused the picture considerably in recent years has been the marketing of the non-benzodiazepine hypnotics, zaleplon, zolpidem and zopiclone. Collectively, these are referred to as the "Z-drugs". In theory, they represent a major breakthrough. Although chemically different from benzodiazepines, they target the same gamma-aminobutyric acid type A ($GABA_A$) receptors, but with varying degrees of selectivity.[16] Benzodiazepines bind non-selectively at both the $_1$ (associated with hypnosedative effects) and $_2$ receptors (associated with effects on memory and cognitive functioning). Zolpidem and zaleplon are highly selective for $_1$ receptors, while zopiclone is somewhat selective. All three have a short half-life (ranging from 1 to 6.5 hours). However, despite these apparent advantages, the Z-drugs have all been associated with daytime sedation, tolerance and the development of dependence, the very problems associated with the benzodiazepines.

In terms of efficacy, meta-analysis has shown no significant difference between the effect on sleep latency between benzodiazepines and zopiclone (based on three trials, n = 96), although slightly longer sleep has been shown with the benzodiazepines (23.1 minutes, 95% CI 5.6-40.6).[11] In four trials (n = 252) there was a non-significant trend towards more side effects with the benzodiazepines than with zopiclone (odds ratio 1.5, 95% CI 0.8-2.9), but also a trend towards a lower dropout rate with the benzodiazepines.

Despite often-breathless claims made in respect of the new drugs, the balance of evidence now points to their being little different from the shorter-acting benzodiazepines. Recently, the United Kingdom's National Institute for Clinical Excellence (NICE) completed a major review on the place of the Z-drugs in therapy.[17] The full technical report on which this advice is based in available on the NICE web site (), which contains extensive comment on the available evidence, with particular emphasis on the elderly, as this is the group in which hypnotic use is greatest (particularly in women) and in whom the consequences of daytime sedation can be most dire. The bottom-line advice (based on data from 24 RCTs) from NICE could not be stated more baldly: "It is recommended that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed." This is preceded by the statement that "hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications". All the trials considered were of short duration (one night to six weeks). Only five of the 24 trials were conducted in the elderly (60 years or older), although another 12 did not exclude elderly participants. In all but three of these trials, the elderly were given standard doses of either the benzodiazepines or the Z-drugs.

Determining the potential for dependence and abuse is often difficult, and the NICE review also cautioned against a simplistic interpretation of the paucity of information in the reported cases. A 2002 review found 36 cases of abuse of and dependence on zolpidem and 22 cases in relation to zopiclone reported in the literature.[18] This was contrasted with the volumes of each product sold in Europe, Japan and

Table I: Relative prices of hypnotics

Hypnotic drug	Dose for the elderly or lowest recommended daily dose (available dose)	SEP per recommended dose (excluding VAT)
Loprazolam	0.5mg (2mg)	R1.26 (innovator)
Lorazepam	1mg (1mg)	R1.32 (innovator)
		R0.71 (generic)
Lormetazolam	0.5mg (1mg tablet from	R1.73 (innovator)
	innovator, 0.5mg capsule	R4.76 (generic)
	from generic manufacturer)	
Temazepam	10mg (10mg)	R2.53 (innovator)
Midazolam	7.5mg (7.5mg)	R2.87 (innovator)
(Triazolam)*	0.0125mg (0.0125mg)	R1.51 (innovator)
Zopiclone	3.75mg (7.5mg)	R2.57 (innovator)
Zolpidem		R0.40 (generic)
	5mg (10mg)	R2.11 (innovator)
		R0.86 (generic)

* not recommended

the United States, and the claim was made that the relative incidence of reported dependence was similar for both drugs, but "remarkably lower than that of benzodiazepines". Tolerance was clearly shown, with doses of 30-120 times the recommended dosage being consumed. As usual, it was noted that "patients with a history of abuse or dependence and those with psychiatric diseases seem to be at increased risk". Anyone who has read Charles Medawar's classic book, "Power and Dependence", will recognise the phenomenon.[19] His advice remains pertinent: "Differences between benzodiazepines are much less important than how they are prescribed and taken". In this regard, the Z-drugs can be included in the same breath. As Medawar puts it: "Newer drugs, almost always seemingly safer than they really are, will always tend to be prescribed as if they could do no harm – too much to ask of any potent drug".

Cost-effectiveness

The NICE review included comments on two industry-submitted economic models that tried to show that the increased acquisition costs of the newer agent (in both cases zaleplon) were offset by potential savings associated with lower consumption of healthcare resources (in one case associated with fewer road traffic accidents related to residual daytime effects, in the other with fewer hip fractures). The manufacturer of zopiclone also made mention of possible savings from a reduced incidence of high-cost dependence. These arguments were rejected, and a cost-minimisation approach was suggested.

The UK National Health Service provides loprazolam, lorazepam, lormetazepam and temazepam as their "shorter" half-life drugs. In South Africa, midazolam and triazolam are also available. Concerns about the safety of triazolam must be noted, however. The following table shows the locally registered doses, with the suggested dose for the elderly reflected (or the lowest recommended daily dose) where possible, and the current single exit price per dose (excluding VAT). In each case, it is assumed that the lowest dose can be obtained by splitting the available tablet formulation (at worst into quarters). Tablet splitting is not always easy for elderly patients, which may limit its usefulness. The available strengths are also shown.

If the same principle as espoused for the UK is applied here – choice of a shorter-acting agent based on acquisition cost alone – then the lowest cost option would be a generic form of zopiclone.

Conclusion

Finding a truly evidence-based approach to the management of insomnia in the elderly is not without problems. As has been shown here, evidence for the efficacy of non-pharmacological methods is severely lacking. Evidence for the efficacy of the benzodiazepine is also remarkably modest, given its widespread use. This lack of evidence is related partly to the lack of a validated measure of global benefit and risk. As expected, few trials have been done specifically with the elderly, and also specifically using the lower doses suggested for use by this group. While theoretically attractive, the newer non-benzodiazepine hypnotics also lack strong evidence of superiority over the older agents. This means that the choice of hypnotic, if it is to be used at all, can be made on the basis of the acquisition cost alone. Such agents are only to be used when sleep hygiene and other non-pharmacological measures (including appropriate physical exercise) have failed. Even then, they should be used at the lowest possible dose, preferably given intermittently, and for no more than two to four weeks. However, before any interventions are tried, a serious attempt must be made to identify any underlying medical condition or drug use (including alcohol) that may be contributing to the problem so that the cause itself can be addressed. Finally, in any patient for whom a hypnotic is prescribed, whether benzodiazepine or non-benzodiazepine, there must be prior consideration and discussion with the patient of how use of the agent will be stopped. There is no evidence at all to support the ongoing, chronic use of these agents by any patients, least of all by the elderly.

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