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Effects of Hypnotics on Sleep and Quality of Life in Insomnia

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Summary This chapter provides an overview of the effects of hypnotics on sleep and quality of life (QOL). In the 1970s it was accepted that a consequence of taking longer acting benzodiazepine hypnotics was a residual hangover next day, producing feelings of sedation and impaired performance. The realization during the 1980s that insomnia was not just a subjective complaint of poor sleep, but in itself resulted in impaired functioning with increased accident risk, led to studies evaluating the effects of sleep medication on both sleep and waking function including QOL. The potentially impairing effects of hypnotic treatment therefore need to be weighed up against the costs and consequences of untreated insomnia. The emergence of the newer benzodiazepine receptor agonists (BzRAs) zopiclone, zolpidem and zaleplon (Z drugs) with their shorter half-lives and reduced levels of residual impairment, tolerance and dependency, particularly for zolpidem and zaleplon, shift the balance in favour of safer hypnotic treatment, so that insomnia should no longer go unrecognized and untreated in so many. Guidelines for limiting hypnotic prescriptions to a few weeks resulted from the association of long-term benzodiazepine use with tolerance and therefore lack of treatment benefit, as well as the associated risks of dependence occurring with some compounds. These guidelines are at odds with the significant number of chronic insomniacs, often elderly patients, who require long-term treatments. There is now limited evidence that newer formulations and different treatment schedules, including intermittent use, can sustain hypnotic efficacy with the Z drugs over longer periods, enhancing QOL and waking function, and without rebound insomnia following withdrawal. Similarly, behavioural and psychological approaches may be beneficial in the long term for some, though possible treatment limitations amongst different types of patients have still to be defined.

Keywords Benzodiazepines · residual effects · accidents · newer benzodiazepine receptor agonist (Z-drugs) · improved waking function · behavioural and psychological treatments

Learning objectives:

- Benzodiazepine hypnotics, particularly the longer acting ones, are associated with residual impairments of waking function next day.
- The elderly, in whom insomnia is more prevalent, are more vulnerable to the impairing effects of benzodiazepines and are at greater risk of accidents and falls as a result.
- Withdrawal of benzodiazepine and Z-drug hypnotics can produce rebound insomnia.
- Benzodiazepine use is also associated with dependency.
- Withdrawal from chronic benzodiazepine hypnotic use is associated with improved waking function and quality of life.
- Behavioural and psychological treatments are useful for the treatment of chronic insomnia and withdrawal from long-term benzodiazepine use.
- The newer benzodiazepine receptor agonists or 'Z-drugs' have shorter half-lives and are associated with reduced residual effects, particularly zaleplon and zolpidem which are the shortest acting. However, they may not be so effective for sleep maintenance problems.
- Newer formulations of the Z-drugs (eszopiclone and zolpidem-MR) may be effective for both sleep initiation and maintenance problems, as well as having reduced residual effects.
- The Z-drugs are associated with improved waking function and quality of life in patients with insomnia.

From: J. C. Verster et al. (eds.): *Sleep and Quality of Life in Medical Illnesses*

Introduction

Looking back over the last 30 years to when the authors first began in sleep research provides an interesting perspective with which to evaluate the use and effectiveness of hypnotics in the treatment of insomnia and their impact on quality of life (QOL). Whilst earlier studies dating from the 1950s had focussed on effects of these drugs on sleep, studies from the 1970s began to include assessment of residual effects next day (1).

Research from the beginning of this period included assessments of the then newer benzodiazepines, perhaps comparing them to the older barbiturates. Studies typically involved normally sleeping participants with sleep assessment largely based on subjective measures and a variety of daytime performance tests borrowed from the psychology laboratory to see whether the sedative drugs were still impairing performance next day (1–4). The view at this time was that residual impairment may be a necessary result of effective hypnotic treatment (2). Whilst benzodiazepines replaced the barbiturates for safety reasons, shorter acting benzodiazepines such as triazolam were then introduced in an attempt to limit the morning 'hangover'. Concerns over dependency, tolerance and the search for shorter acting drugs producing less or no residual impairments next day have resulted in the emergence of the 'Z' drugs also described as the newer benzodiazepine receptor agonists (BzRAs). The first was zopiclone, followed by zolpidem and then zaleplon, each with a shorter half-life. With zaleplon, a half-life of around 1 h means that this drug can be taken during the night, up to 4 h before waking, without detectable residual impairments (5, 6). This provides the opportunity for responsive treatment as required rather than prophylactic administration 'in case' of a bad night. We have also seen the arrival of the first 'non-scheduled' hypnotic in the USA, ramelteon, which is a melatonin receptor agonist for use in sleep onset insomnia, and developments continue with other GABAergic drugs which do not act through the benzodiazepine receptor such as gaboxadol (7) and tiagabine (8).

Has this evolution in hypnotic drugs met the needs of insomniacs and the needs of physicians treating their patients? If sleep can be improved has this solved any QOL problems that may ensue as a result of poor sleep? Recent publications indicate that the antidepressant trazodone is the most widely prescribed drug used for the treatment of insomnia in the USA and that hypnotic prescriptions have been falling over the last decade (9, 10). This evidence alone suggests that the needs of patients and physicians have not yet been met with the 'perfect' hypnotic as outlined by Bartholini nearly 20 years ago (11).

This chapter provides an overview of the current situation regarding hypnotic treatment for insomnia, focusing on health-related QOL aspects. A brief comparative review of selected papers that look at the effect of hypnotics on the sleep and waking performance in insomniacs is included. The final sections look at the treatment of insomnia with hypnotics and emerging alternative treatments, with a view to optimizing QOL.

Who are the Patients?

Whilst most studies of hypnotics have employed 'normal' male volunteers, as is frequently the case in central nervous system (CNS) drug development, insomniac patients complain of problems sleeping, or poor sleep quality and unrefreshing sleep, together with fatigue and tiredness and impaired functioning during the day. In fact, impairment of daytime function and impairment of related QOL aspects has been used to aid assessment of severity and the decision to treat this essentially 'subjective' complaint (12). Similarly, the majority of insomniacs are women (13–15) with the prevalence increasing with advancing age (16–18), with up to a quarter or a half of those aged 65 and older having insomnia (18–20) although normative data indicate a median sleep duration of 7 h in the elderly (21). It is also worth noting that the elderly are more affected by sleep maintenance problems whilst the young suffer more from sleep initiation difficulties (19) and this too has implications for hypnotic treatment. Regrettably, the focus of hypnotic studies has not been on the elderly or women rather than men. Epidemiological studies suggest that somewhere around 10–15% of the population have persistent or chronic insomnia (22–24). Figures for insomnia and related sleep problems often suggest higher figures of 30–40% (25–27) but may well reflect variability in the criteria used to assess this condition where even a chronic insomniac may not have problems sleeping every night. This lack of a standardized definition has had a negative impact when trying to compare studies of both pharmacological and non-pharmacological treatment approaches though standardized criteria have now been proposed and this should benefit future research (28, 29).

What we do know is that hypnotic use reflects the greater prevalence of insomnia in women rather than men and in older rather than young adults (19, 30–38). Frighetto et al. (17) reported that a third of patients, who were mostly in their eighth decade, admitted to hospital had received antidepressants or hypnotics prior to hospital admission in their Canadian study. Further, the elderly may have a greater need for long-term treatment and may well be more vulnerable to the impairing effects of sedative hypnotics drugs (16, 39, 40). Whilst clinical guidelines generally indicate limited periods for prescriptions (e.g. 2–4 weeks depending on the country), 14–35% of patients may have used them nightly over the previous year (41).

It is also important to recognize that whilst nearly everyone will experience some sleep disturbance in the course of a year and some will continue to have sleeping difficulties for months or years afterwards. When we carried out a local survey of university employees with sleep problems, it indicated that

approximately half of these respondents had their problem for up to 6 months whilst the rest had a lasting problem, some up to 20 years. The Europe-wide SOFRES study found a median duration of 2–6 years (42). The long durations reported for insomnia led Epstein and Bootzin (43) to proclaim that these long suffering patients were 'in dire need of treatment'. This raises further questions of why should insomnia persist so long in those who develop chronic insomnia and are hypnotics of any use for long-term treatment?

Several authors have pointed out that patients, including the elderly, may not report their insomnia to their healthcare providers, and consequently the condition may not be recognized and will go untreated (18, 31, 44, 45). Sateia et al. (46) reported that between 30 and 80% of patients show no significant remission over time and that 70% of patients do not discuss their problem, a finding supported by Kageyama et al. (31), who suggested that 80% of Japanese insomniacs were untreated. Having witnessed the concern over benzodiazepine dependency in the 1980s, including public demonstrations in Europe, it was hardly surprising to see that hypnotic prescriptions fell from 1970 to 1989 reflecting these concerns and those of the prescribing physicians (47) although higher rates may be seen in some countries with Byles and colleagues reporting that in Australia half of their sample of older women with sleeping problems were receiving medication in the last month (30). These concerns and the resulting limitations imposed on treatment duration may partially explain why prescription hypnotics are not the most used or prescribed treatments for insomnia and why the antidepressant trazodone is the most widely prescribed 'hypnotic' in the USA (9) despite a relative lack of appropriate studies demonstrating efficacy (9, 10, 40). This in itself is remarkable given the sedative nature of this drug and its impairing effects on performance and impairment of sexual function (48, 49).

The association between insomnia and depression may in part help to account for the widespread use of trazodone although the use of sub-therapeutic doses of antidepressants as hypnotics may also result from the reluctance to use benzodiazepines long term although studies of their efficacy are more limited (10, 24, 40, 50–52). Thase (10) points out that ideally monotherapy would be used to treat both insomnia and depression, although at present no suitable drug exists. The close links between mental disorders such as anxiety and depression and insomnia emphasizes the need for appropriate treatment, half of patients with chronic insomnia have a primary psychiatric disorder such as anxiety or depression (10, 53). Insomnia has been considered as a possible prodromal phase for depression and although authors stop short of claiming that insomnia causes depression, the fact that untreated insomnia increases the likelihood of developing clinical depression is clearly established (54–57). Similarly, improvement in depression may parallel improvements in insomnia (10,58–60) though this may reflect a negative cognitive bias associated with depression itself (61, 62). Subjective sleep improvement has also been linked to phase-shifts in sleep for these patients (63). However, these links should be considered when evaluating the effects of hypnotics on QOL and the relative merits of hypnotic treatment.

Before looking at the specific effects of hypnotics on relevant QOL aspects including mood and performance, it is useful to briefly consider the effects of insomnia itself on QOL, though fully described elsewhere in this volume, to provide a comparison. If hypnotics have negative effects, then is it worth using them or would it be better to leave insomnia untreated? Following on are the questions of whether all hypnotics are the same and how do they compare to other treatments?

What are the Costs and Consequences of Insomnia?

Whilst early studies of benzodiazepines focussed on their potential to improve sleep and possibly their effects on waking performance next day, there was a shift in research during the last decade recognizing the importance of health-related QOL and its relevance when considering insomnia and disturbed sleep (64, 65). The wake up call probably came in 1988 when Damien Leger published figures suggesting that of the US accident costs for 1988 ($50 billion) around a third may be sleep related (66). This helped to focus attention on the wider significance of sleep disorders as well as their treatment. There have been a range of estimates for the annual costs of insomnia including $14 billion direct costs and $80 billion for indirect costs (67, 68), and $30–35 billion by Chilcott and Shapiro (69) comprising direct costs (health care provision) and indirect costs such as absenteeism and accidents (70,71). Consequently, there is now the realization that there is a critical duration of sleep needed to ensure health and safety (72, 73).

These figures alone show that it is important to treat insomnia as the cost to both patients and society will in turn affect QOL through reducing available resources. Further, the finding that falls in the elderly are related to insomnia and tiredness is important to bear in mind when considering the relative merits of hypnotic treatment (74). General costs and consequences include increased daytime sleepiness and fatigue leading to cognitive impairment and poor work performance and absenteeism in addition to increased accident risk including driving, increased risk of new or recurrent psychiatric disorder and increased substance use, poorer prognosis, increased healthcare-related financial burden and poorer social functioning at work and at home (10, 13, 22, 24, 55, 66, 68, 70, 75–77).

Apart from the more drastic consequences of insomnia with daytime sleepiness and fatigue resulting in impaired performance and accidents, recent research has indicated the role of sleep in memory consolidation (78), and this may partially explain the association of disturbed and insufficient sleep with poorer academic performance (79, 80). Recently, two groups

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have shown a relative impairment in memory consolidation for insomniacs in comparison to normal sleepers (81, 82).

The 'SF-36' is perhaps the most well-known questionnaire-based QOL measure used in insomnia research though several exist including a specific 'quality of life in insomnia' (QOLI) scale (83). However, Buysse and colleagues recently described the use of the SF36 as 'essential' for insomnia research (28). The SF36 comprises eight dimensions: physical and social functioning, role physical and mental, energy/vitality, pain, mental health and health perceptions. The authors were involved in evaluating the findings of Europe-wide SOFRES study (42, 84), which indicated reductions for role physical, energy, vitality and mental health. These reductions fell outside the normal ranges established for the SF36 (85). These findings were supported by the significant reductions in emotional, social and physical domains found by Zammit et al. (86). Several studies have found reductions in QOL dimensions associated with insomnia, including greater reductions in SF36 with increased severity of insomnia for physical and social functioning, energy/vitality, mental health and general health perceptions (24, 87). This increased reduction in QOL with increased severity of sleep problems has also been observed for older women insomniacs (30), the patient group in whom insomnia is most prevalent. Research with other instruments has indicated increased functional impairment and healthcare costs in insomnia (88) and associated reductions in QOL (25, 45). A reduced QOL in the elderly with insomnia has also been reported (34, 36).

Taken together, these findings show that insomniacs are not just troubled by inadequate or un-refreshing sleep, with consequent feelings of tiredness and fatigue during the day, but that this in turn translates into significant health risks and costs, with poorer life performance affecting both work and home. Further, there is a significant financial burden attached as well as increased injury and mortality as a result of accidents. It is then remarkable that insomnia frequently goes unreported or untreated.

Do Hypnotics Improve Waking Function?

Given the above, there is a clear imperative to treat insomniac patients, whether they are primary insomniacs or whether their insomnia is related to another illness or associated with a mental health problem.

The earlier studies investigating benzodiazepines clearly established the residual effects associated with benzodiazepine use, particularly for the longer acting compounds or those with long-acting metabolites. Not only did the morning 'hangover' affect mood and subjective feelings of alertness but aspects of performance including speed of psychomotor response as well as memory were impaired (89–94). These findings, presented in numerous publications, together with concerns over dependency and tolerance associated with some chronic benzodiazepine usage and the realization that their continuous use did not improve the sleep of insomniacs and that withdrawal may itself produce insomnia and related adverse effects (95–103) led to the development of the newer benzodiazepine receptor agonists or BzRAs, zopiclone, zolpidem and zaleplon by the pharmaceutical industry (104–107). In comparison to the traditional benzodiazepines, these compounds are associated with a more natural sleep profile, e.g. without the reductions in slow wave sleep seen with benzodiazepines (50) and generally associated with a lower abuse potential and less residual effects, particularly zolpidem and zaleplon (23, 44, 108–111), leading to improvements in insomnia management (112).

Accidents and Car Driving

Laboratory performance assessments provide useful direct comparisons and models of every day life with which to compare a therapeutic class of compounds such as hypnotics. However, possible real life dangers associated with hypnotic consumption may be reflected in accident figures and driving assessment. Increased traffic accident risks have been associated with benzodiazepine use and an increased risk has also been found with zopiclone. Similarly, increased falls and associated injuries as well as increased traffic accidents have been linked to benzodiazepine use in the elderly (113–122).

The increasingly shorter half-lives for zopiclone (over 4 h), zolpidem (2 h) and zaleplon (1 h) have been reflected in their relative degree of residual impairment. The traditional benzodiazepines, particularly those with longer half-lives and longer acting metabolites are associated with greater impairment and sustained residual effects (23, 123–125). However, reviews also indicate that some of the shorter acting compounds are not associated with the same degree of impairment. For example, Puca et al. (126) reported improved sleep and QOL and no residual effects with triazolam given to shift-work syndrome patients.

The elderly are more vulnerable to the impairing effects of sedative drugs, particularly the longer acting ones, yet they receive more benzodiazepines and with more chronic use (35, 36–38, 39), and this is also reflected in falls and related injuries. Stein and Barrett-Connor (127) reported a reduction in QOL in the elderly associated with the use of medication including hypnotics that went beyond the impact of the comorbid illness. On the other hand, Ring (18) reviewed chronic insomnia in the elderly and noted that early recognition and treatment of insomnia would increase QOL, particularly as the condition is under-recognized in these patients.

When compared with the lower incidence of side effects in general for the Z-drugs and substantial lack of residual effects for zaleplon and zolpidem in particular, then a clear distinction can be made (23, 128–130). Recent reviews of driving studies have shown that both zaleplon and zolpidem lack residual effects when assessed with both simulated and on the road driving (131, 132). Given the clear association between insomnia, increased tiredness, sleep loss and driving

accidents (75, 77, 133), the lack of residual impairments in driving performance next day is an important indicator of the potential benefits of zaleplon and zolpidem on functional aspects of QOL.

The introduction of the newer BzRAs or Z-drugs has therefore provided something of a watershed in relation to pharmacotherapy for insomnia. The older benzodiazepines were frequently associated with residual impairments next day, which had a negative impact on QOL affecting waking mood, work performance and accident risks. The elderly in whom insomnia and benzodiazepine use is increased are most vulnerable here, with reduced hepatic clearance and other age-related impairments potentially exacerbating residual effects.

Studies of the effects of the Z-drugs on sleep, daytime alertness and performance, or related QOL aspects in insomniacs show that they are not associated with the degree of impairment seen with the benzodiazepines. Goldenberg et al. (134) reported significantly improved QOL in insomniacs after 2 weeks zopiclone in comparison to placebo. Leger, Quera-Salva and Philip (135) looked at both short- and long-term administration of zopiclone in insomniacs. Both sleep and QOL were improved at 8 weeks against placebo. No significant differences were found for patients who had been taking zopiclone for 12 months when compared to controls without sleep problems on nearly all QOL measures, suggesting that QOL can be normalized in insomniacs given appropriate hypnotics.

An investigation of eszopiclone, the (S)-isomer of racemic zopiclone, in elderly insomniacs revealed improved sleep, increased daytime alertness, physical well-being and other QOL variables, in addition to reduced napping (136). This contrasts with reductions in QOL found in insomniacs with increased daytime sleepiness and napping (25), demonstrating the ability of Z-drugs to promote a functional increase in daytime alertness when given to insomniacs. Soares et al. (137) found that eszopiclone improved both subjective sleep and QOL in women insomniacs. These brief examples demonstrate the ability of Z-drugs to both improve sleep and improve waking function when given to insomniac patients, including both short and long-term administration.

The results of systematic reviews of sleep, performance and related QOL measures with strict inclusion criteria, contrasting traditional benzodiazepines and the newer Z-drugs in carefully controlled patient trials have not been able to make firm conclusions due to the limited number of studies compared (138).

Studies of daytime function using psychomotor performance tests in healthy volunteers after hypnotic drug administration have been very useful in indicating behavioural toxicity, as seen above, and impairments have been seen after single doses of even short-acting agents. However, similar measures in insomniac patients have been less conclusive. Table 7.1 summarizes controlled studies of hypnotic drug effects on performance in patients. This includes some traditional benzodiazepines, the newer Z-drug hypnotics, as well as single examples for the GABA agonist tiagabine and melatonin agonist ramelteon. The studies in the table reflect the general findings from past research where the benzodiazepine flurazepam was deliberately chosen as a comparator for newer compounds as it is has the longest half-life (up to 250 h) and can serve as a positive control. Flurazepam reliably impairs performance next day whilst the Z-drugs or short-acting benzodiazepines may not although simulated driving performance was impaired by zopiclone as mentioned earlier. Whilst reliable deficits were seen with flurazepam other findings are less consistent than those in healthy volunteers. One explanation may be that these patients differ markedly from controls at baseline, in that they complain of fatigue, diminished motivation, cognitive dysfunction including reduced vigilance, memory and concentration, low mood and various physical complaints so that impairing effects of drugs may be less obvious. It may be that as these patients had been taking the treatment for some days or weeks, early impairment may have worn off by the time of testing.

Though limited in number, these studies endorse the conclusions made above that the newer Z-drugs are less impairing than older long-acting compounds, favouring their use over the older benzodiazepines with their related dependency, tolerance and withdrawal problems. To date, studies with the newer agonists tiagabine and ramelteon have been too few to draw specific conclusions.

Sleep Initiation and Maintenance

Given the variability in both the frequency of occurrence of disturbed sleep, as well as patient differences relating to problems in initiating sleep, maintaining sleep or waking early, it is important to consider which hypnotics are most suited to aiding sleep onset and which can also maintain sleep. With the benzodiazepines, longer acting compounds produced consistent residual impairment leading to the search for shorter acting but less impairing compounds on waking performance next day (139). This has been reflected in the development of the Z-drugs with even shorter half-lives. Whilst they produce less residual impairment, there is a trade-off resulting in reduced efficacy of the shorter acting zaleplon (1 h half-life) and zolpidem (2 h half-life) with regard to sleep maintenance. On the other hand, zopiclone (>4 h half-life) may produce significant waking impairment but is more appropriate for sleep maintenance problems (10, 40). The newer derivatives may be a response to this. Eszopiclone may promote sleep maintenance but with reduced potential for impairment, whereas modified release zolpidem (zolpidem-MR) may also increase sleep duration though studies are currently limited (136,140–142). The limitation of the shortest acting Z-drugs zaleplon and zolpidem in treating sleep maintenance problems is a potentially significant drawback to their use. It is also worth reflecting that more sleep onset insomnia

TABLE 7.1. Controlled studies of hypnotic drugs in insomnia.

Reference	Design	Patients	N	Drug	No. of nights	Improved sleep?	Test time (hours after dosing)	Tests	Performance results
175	DB II group	3/12 insomnia	30	Zopiclone 7.5 mg, flurazepam 30mg, placebo	10	Y (subj)	11	DSST immediate and delayed, recall, movement	Flurazepam-impaired movement
176	DB II group	Elderly insomniacs	36	Brotizolam 0.25 mg, flurazepam 30 mg	14	Y (subj)	12	DSST immediate and delayed, recall, movement	Both drugs impaired all (authors comment doses too high). Impairment recovery proportional to half-life
177	Single-blind	Chronic insomnia (all had past hypnotics)	6	Placebo run-in, zolpidem 10 mg	14	Y	8.5	Memory, manual dexterity, maze, DSST	No impairment
178, 179	DB II group	Chronic insomnia, recruited by advertisement	107	Placebo run-in flurazepam 15 mg, 20 mg midazolam 15 mg	14		9	DSST, vigilance, divided attention, mood	Flurazepam 20 mg impaired all, slight impairment with 15 mg, none with midazolam
180	DB PC II group	Insomnia, unable to sleep without medication	26	Zopiclone 7.5 mg or flurazepam 30 mg or placebo	35		Not stated	CFF, CRT, digit span	CRT and digit span impaired by flurazepam
181	DB 5-way II group	Age 65+ DSMIIIR insomnia with TST < 5 hand/or #w > 3 for 3 months	45	Temazepam 15 and 30 mg, triazolam 125 and 250 μg, placebo	Single dose	12		Wechsler verbal memory tasks, DSST, trail-making, finger-tapping on mornings before and after dose night	Significant impairment word pair recall with high doses, significant improvement trail-making after low dose, high dose no change

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TABLE 7.1. Continued

Reference	Design	Patients	N	Drug	No. of nights	Improved sleep?	Test time (hours after dosing)	Tests	Performance results
182	DB PC II group	3/12 insomnia	68	Zolpidem 10 mg, 15 mg, placebo	35		Not stated	DSST	No effects (very little subjective effect, small objective effect on sleep)
134	DB PC II group	Recruited through market research organization, TST < 6 h, SOL > 30 min	231/227	Zopiclone 7.5 mg, placebo	14		NA	QOL, subjective sleep	QOL improved both groups, significantly more in zopiclone group, in daily activities, social and professional subscales
183	DB PC CO	Primary insomnia (very similar to DSM IV criteria)	23 F	Zolpidem 10 mg, temazepam 20 mg, placebo at 02.00	30		5.5	Driving simulator 07.30 followed by immediate recall memory test	No sig diffs although a few individual subjects' driving affected badly by both drugs—may be especially vulnerable people? No effect on memory tests
184	DB PC II group	DSM-IV primary insomnia, TST < 7h, SOL > 20 min	308	Eszopiclone 2, 3 mg, placebo	44		1–1.5 h after wakening	DSST	No sig effect
132	DB PC 4-way CO	DSM-IV primary insomnia, recruited by advertisement	23	Zolpidem 10 mg, zopiclone 7.5 mg, lormetazepam 1 mg, placebo	7		2 h after waking	Driving simulation	Lormetazepam-impaired speed deviation and speed limit deviation. Zopiclone increased number of collisions
8	DB PC CO	DSM-IV primary insomnia, recruited by advertisement	Tiagabine 4, 8, 12, 16 mg, placebo	2	About an hour after waking		DSST and Rey auditory learning test	DSST impaired by 8 and 16 mg	
185	DB PC CO	Treatment seeking plus advertisement	107	Ramelteon 4, 8, 16, 32 mg, placebo	26		Not stated	DSST, word-list immediate and delayed recall	No effects

#w, number of awakenings; CFF, critical flicker fusion frequency; CO, crossover; CRT, choice reaction time; DSST, digit symbol substitution test; II group, parallel group; PC, placebo controlled; RT, reaction time; SOL, sleep onset latency; TST, total sleep time.

is seen in younger insomniacs whilst sleep maintenance problems are more prevalent in the elderly who in turn are more vulnerable to the effects of impairing drugs (19).

Treatment Regimens

Concerns over dependency and loss of efficacy after continuous treatment with benzodiazepines led regulatory authorities to impose clinical guidelines limiting prescriptions. Given the epidemiological data indicating that 10–15% of the population suffer from chronic insomnia and the need of some, including elderly patients for prolonged treatment, treatment guidelines are clearly at odds with patient needs. The development of the newer BzRAs, with a more favourable side effects profile, including reduced dependency potential for some compounds, suggests that guidelines predicated on the benzodiazepines may now be out of date and that longer treatment periods should be considered (14, 24, 143). Sadly, the duration of most controlled studies is relatively short, one meta analysis found a median treatment duration of just 7 days, whereas chronic insomniac patients sometimes use hypnotics for months to years (144,145). Although few in number, some longer term treatment studies have been undertaken. Patient studies with zolpidem have revealed overall improvements (146–149). In a 17-week study of zopiclone, Fleming, Bourgouin and Hamilton (150) failed to find evidence of tolerance, whereas a study of eszopiclone in chronic insomniacs (141) revealed both sustained sleep improvements as well increased alertness and functioning during the day, but without adverse side effects or tolerance over the 6-month study period. A 12-month extension of the study showed comparable efficacy and safety (151). A shorter 5-week assessment of zaleplon (152) found that sleep latency was reduced across treatment weeks, although consistent increases in total sleep time were not seen. There was no evidence of tolerance or rebound insomnia seen on initial withdrawal.

Intermittent treatment has also shown promising results. Intermittent treatment with the benzodiazepine triazolam found reduced self-administration when compared to nightly or as needed treatment regimens (153). Although an 8-week comparison of zolpidem against placebo found improved sleep but failed to reveal significant differences for QOL, a multi-centre 2-week comparison of nightly against 5 out of 7 nights dosing revealed marked QOL improvements in both chronic insomniac treatment groups (154, 155). A more recent review of six patient studies with intermittent zolpidem administration found that sleep improved without adverse effects and hypnotic consumption was not increased. Some studies recorded improvements in QOL measures (44). Studies with zaleplon have indicated the lack of impairment next day with zaleplon when administered during the night, and this might also offer a new treatment regimen where patients can use the drug not only intermittently but on a symptomatic rather than prophylactic basis, waiting to see whether they can fall asleep naturally before taking a hypnotic (5, 6, 23).

Taken together, these studies of long-term and intermittent treatment regimens with the newer BZRAs or Z-drugs suggest that not only can the sleep of chronic insomniacs be improved for sustained periods but waking function and related QOL measures may also be improved. The lack of evidence for dependency or tolerance in these studies implies clinical guidelines might be updated supporting longer administration with associated benefits in QOL. This would help meet the needs of patients who require long-term treatment (10, 40).

Other Treatments for Insomnia

Prescription hypnotics are in a minority when compared to the range of treatments used by insomniacs. The widespread use of trazodone and antidepressants as 'hypnotics' has been mentioned. Other popular pharmacologically based treatments include over-the-counter (OTC) antihistamines, herbal remedies, L-tryptophan, melatonin and aromatherapy (9, 10, 40, 108) although alcohol is also popularly self-administered in the West despite cost, tolerance and toxicity (156). There are also a wide variety of other methods employed including psychological and behavioural therapies, bright light and relaxation therapy as examples. Whilst a fuller evaluation of these cannot be included here, a brief mention is appropriate.

There is limited evidence that OTC antihistamines work although recently some benefits have been reported for diphenhydramine (157). More profound effects on sleep have been reported for both promethazine and hydroxyzine although neither are available as OTC hypnotics (158–160). A recent review of melatonin shows promise for its use for circadian and sleep-phase disorders including shift work (161) although evidence for its use in insomnia is less positive (162).

Several herbal remedies have been investigated, and interest in these compounds is growing though published studies are few (163). Valerian or valerian and hops are popular in some herbal OTC remedies but findings are varied with Morin et al. (157) observing benefits in mild insomnia with valerian and hops whilst Diaper and Hindmarch (164) failed to find significant effect on sleep and performance with valerian alone. A recent review of 16 studies suggested that valerian might improve sleep quality without concomitant side effects (165). Similarly, there is some evidence emerging that aromatherapy may be useful, for example a study by Goel et al. (166) found that lavender not only improved sleep but also increased slow wave sleep which may be of particular benefit to the elderly whose slow wave sleep is reduced. Lewith et al. (167) have found that lavender oil reduced mild insomnia, and Komori et al. (168) found mixed fragrance assisted withdrawal from long-term benzodiazepine use in insomniacs.

Whilst more controlled studies are required for these alternative or complementary remedies, if efficacious, they may offer some advantages. Unlike many prescription medications, they may have reduced side effects and residual impairments next day. This is of particular importance for the elderly who may require longer treatment and who frequently suffer from other illnesses that may require medicines. Therapies that are free from adverse side effects, and possible drug interactions, may be of particular benefit and significantly improve not only sleep but resulting QOL.

Cognitive and behavioural therapies (CBT) are worth particular mention as there benefits are being increasingly recognized although they may not be suitable for all insomniac patients (10,40). The negative effects of long-term benzodiazepine treatment, particularly in the elderly, has been outlined. Withdrawing patients can therefore provide benefits. In a study of elderly long-term benzodiazepine users in whom over 60% had continuously used their hypnotics for over 10 years, 80% were successfully withdrawn from their treatment at 6 months after tapering their dose. The withdrawers showed improved waking performance in comparison to the continuers but showed little by way of sleep differences or withdrawal problems (95).

Studies using CBT have also been successful in helping withdraw long-term benzodiazepine users from treatment and in maintaining improved sleep. Dixon, Morgan and colleagues noted decreased QOL at baseline in long-term hypnotic users, although the decrement reduced with advancing age (169, 170). At 3 and 6 months, sleep and QOL were improved, with sleep improvements and reduced hypnotic use maintained at 12 months follow-up. Reviews by Morin and colleagues has emphasized the reliable and durable effects that can result from behavioural treatments (171, 172), with Epstein and Bootzin (43) emphasizing that non-pharmacological treatments can make a substantial contribution to QOL for insomniacs. Authors have pointed out that the psychological and behavioural treatment approach takes time, as well as significant resources which may balance over long-term treatment, so that efficacy is delayed in comparison to drugs that may be more appropriate for short-term treatments. Further, not all patients may be suitable for CBT approaches, Morgan and colleagues found that patients with higher levels of distress at onset had poorer outcomes (10, 16, 40, 170, 173). Similarly, McCrae et al. +174) found that sleep hygiene practices did not differ between good and poor elderly sleepers suggesting this approach may have limitations in the elderly.

Conclusion

The current interest in medicinal treatments and QOL reflects developments in psychopharmacology. Where as past treatments were focussed on reducing deficits, present research looks more toward optimizing function and even enhancing performance. Thirty years ago, it may have been sufficient to treat disturbed sleep and insomnia with a sedative hypnotic compound and accept residual impairments next day as a consequence of improving sleep. Newer hypnotic compounds including the Z-drugs provide us with important treatment options when weighing up the cost benefit ratio for a particular patient. We know that prolonged and untreated insomnia is associated with impaired QOL as well as substantial costs to society as a result of direct health costs and indirect costs through accidents and absenteeism. Although the shortest acting of the Z-drugs may not be suitable for treating sleep maintenance problems, they show significantly reduced side effects and residual impairments, with improved QOL, and should be promoted over the older benzodiazepines as appropriate drug treatments for insomnia (113). The emerging hypnotics and newer formulations for the Z-drugs (eszopiclone and zolpidem-MR) hold promise for treating both sleep onset and sleep maintenance problems without compromising QOL, and prolonged treatment may now be acceptable.

Where possible, long-term drug treatment for insomnia should be avoided, with cognitive and behavioural therapies providing useful alternatives and aiding withdrawal from long-term benzodiazepine use resulting in improved sleep and QOL. However, the range of application and possible treatment limitations of these treatment approaches needs to be further explored. Similarly, studies of alternative and complementary therapies need progressing to establish the efficacy and range of application for treatments such as herbals and aromatherapy.

With the current range of hypnotic treatments, there is no longer an excuse for insomnia to go unreported and unrecognized and untreated in so many patients including the elderly. Further, shorter-term insomnia should be treated to help prevent the transition to chronic insomnia with its associated marked impairments in quality of life.

Issues that need to be addressed by future research:

- Further studies are required to assess the impact of long-term administration of the Z-drug hypnotics on sleep and waking function in chronic insomniacs, including the elderly.
- The range of patients and types of insomniacs that are effectively treated with behavioural and psychological therapies needs to be established.
- The effectiveness of alternative therapies including aromatherapy and herbal remedies needs to be established but may provide useful alternatives to prescribed hypnotics.

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Chapter 7

Query No.	Page No.	Line No.	Query
AQ1	51	23	The references are been renumbered in order to maintain sequential order. Please check.
AQ2	52	08	The sentence ”The SF36 comprises eight dimensions” states that there are eight dimensions. But only six seem to be listed. Please check.
AQ3	53	Table 1	Please clarify whether the text “(authors comment doses too high)” should be deleted from the table.
AQ4	58	37	Please update the page ranges for reference 12.
AQ5	60	47	Please update the page ranges for reference 98.
AQ6	61	51	Please update reference 134.