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A Comparative Assessment of the Risks and Benefits of Zopiclone

A Review of 15 Years' Clinical Experience

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Abstract

Zopiclone is a cyclopyrrolone hypnosedative that is chemically unrelated to the benzodiazepines but nevertheless potentiates γ-aminobutyric acid–mediated neuronal inhibition, and has demonstrated proven efficacy and good tolerability in the treatment of insomnia over 15 years of use. Zopiclone is indicated for short term use, and should not be prescribed for more than 4 weeks.

This review compares the efficacy of zopiclone with that of a number of commonly used short-, medium- and long-acting benzodiazepines. Zopiclone at dosages of 7.5 mg/day has demonstrated efficacy equivalent and in some cases greater to that of flurazepam 30 mg/day, nitrazepam 5 mg/day, flunitrazepam 1 to 2 mg/day, temazepam 20 mg/day, triazolam 0.125 to 0.5 mg/day and midazolam 15 mg/day. Zopiclone-treated patients reported themselves to be less impaired by daytime sedation than patients treated with the medium- and long-acting hypnosedatives flurazepam, nitrazepam and flunitrazepam. Zopiclone and temazepam showed similar effects on daytime behaviour while zopiclone appeared to have somwhat better effects on daytime well-being than the short-acting triazolam and midazolam. There has been no clinical comparison with the frequently used medium-acting benzodiazepines lormetazepam and brotizolam and the imidazopyridine hypnosedative zolpidem. Data from clinical trials, pooled analyses and postmarketing surveillance including over 30 000 patients showed that with the exception of bitter taste (reported by <10% of zopiclone recipients), the tolerability profile of zopiclone is similar to that of

placebo. Clinical trials found no evidence for significant rebound insomnia and indicated that the risk of withdrawal reactions with therapeutic doses of zopiclone is very low. In addition, to date, dependency appears very low, although abuse potential should be considered following a history of addiction or psychiatric illness. Evaluation of the accumulated evidence from over 2.5 billion units dispensed in more than 30 countries indicates that zopiclone is effective, well tolerated and an excellent alternative to benzodiazepines in the short term treatment of insomnia.

Insomnia is estimated to affect about one-third of the general population, with up to about one-quarter of those affected experiencing severe sleep deficit.[1-4] These proportions are considerably higher in the elderly. Poor sleep imposes significant personal and social costs: it is associated with poor concentration, memory problems and irritability, as well as increased morbidity and negative consequences on health-related quality of life, daytime well-being and the economy.[5-8] Recent conservative estimates from the early 1990s of the financial costs of insomnia range from $US92.5 to 107.5 billion for the US alone.[9] Appropriate and effective management of insomnia is therefore an important and pressing concern.

Successful management of insomnia requires a detailed assessment of the patient's medical and treatment history.[10,11] Ample evidence from numerous publications suggests that a multifactorial approach is required for the treatment of insomnia. Treatment of underlying medical conditions and behavioural adaptations – such as stimulant avoidance, exercise and relaxation – should be the primary options for patients with insomnia.[12,13] Patients should be advised to adopt a disciplined approach to sleep, including the avoidance of television and other bright lights before sleep, getting up at the same time of day, and minimising daytime naps.[14] In a number of more severe cases, however, pharmacological treatment is advisable, requiring identification of the agent with the optimal combination of efficacy, tolerability and lack of adverse events both during use and on discontinuation.[15-17]

Benzodiazepines have been regularly prescribed for insomnia since the 1970s. Although they have been shown to be highly effective in the short term, many benzodiazepines are associated with a number of unwanted effects, notably a well documented potential for dependence, residual effects on waking, as well as rebound insomnia and withdrawal reactions after prolonged use.[15,17-22] The occurrence of such effects is often related to the half-life of the benzodiazepine. For example, longer acting agents such as flurazepam and nitrazepam are more likely to be associated with deleterious residual effects the following day, such as subjective feelings of hangover. Short-acting benzodiazepines are less likely to cause residual effects, but have been associated with rebound insomnia, tolerance and amnesia, and may not be as effective as the longer-acting class at controlling early awakening.

The disadvantages and adverse effects of benzodiazepines therefore render them far from ideal agents. The optimal hypnosedative would have the best combination of activity and lack of unwanted effects: it would be effective in rapidly inducing and maintaining good quality sleep, but cause minimal residual effects, impairment of waking activity, dependence or withdrawal. These requirements fuelled the search for improved hypnosedatives, and led to the development of zopiclone. As presented below, zopiclone has well documented efficacy in the management of insomnia, and appears to be better tolerated than most benzodiazepines, causing fewer serious adverse events, fewer daytime effects and fewer problems on discontinuation of therapy.

Zopiclone is a cyclopyrrolone hypnosedative that is chemically unrelated to the benzodiazepines, with an elimination half-life of 5.1 hours.[23] Like the

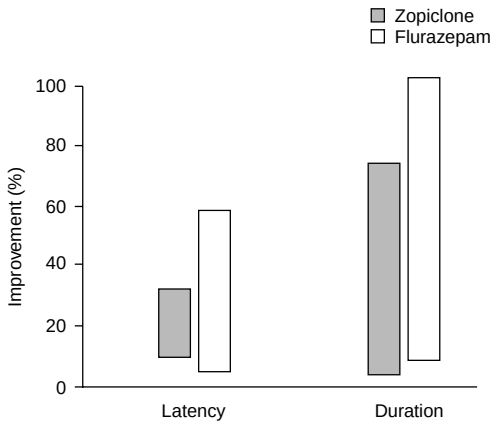

Fig. 1. Range of improvement noted in sleep parameters in patients receiving zopiclone 7.5 mg/day or flurazepam 30 mg/day.[33-35]

benzodiazepines, however, zopiclone binds the type A γ-aminobutyric acid ($GABA_A$) receptors in the brain, and potentiates GABA-mediated neuronal inhibition. Zopiclone binds both benzodiazepine BZ_1 and BZ_2 GABA receptor subtypes. Barbiturates, which are now infrequently prescribed due to their low margin of safety, also bind the same receptor, but at a different site.[24,25]

The efficacy of zopiclone as a hypnosedative in humans was first demonstrated 20 years ago, and has been well established in numerous trials.[26-29] Zopiclone has also been shown to be effective at improving sleep quality in elderly patients.[30-32] This brief review compares the efficacy of zopiclone with that of long-acting as well as medium- or short-acting benzodiazepines, and with the nonbenzodiazepine zolpidem. In clinical trials, such efficacy is commonly assessed by questionnaires and visual analogue scales, on which patients indicate scores for relevant sleep parameters. These include the time taken to fall asleep (sleep latency), the duration and quality of sleep and the patient's overall assessment of subjective efficacy of the drug. The safety of zopiclone use is also discussed with particular emphasis on the potential for rebound insomnia, dependence and withdrawal reactions, residual effects and tolerability.

1. Comparative Efficacy of Zopiclone

1.1 Long-Acting Benzodiazepines

1.1.1 Flurazepam

Zopiclone and flurazepam, a long-acting benzodiazepine, both improve sleep quality and sleep parameters (fig. 1). While some investigators find zopiclone to be superior to flurazepam, others have found similar efficacy.[26] For example, in a study of 36 adults with insomnia, Elie et al.[33] reported that zopiclone 7.5 mg/day, but not flurazepam 30 mg/day, significantly reduced sleep onset latency by 18% compared with placebo, after 3 weeks' therapy ($p < 0.05$). Zopiclone improved sleep duration significantly more than placebo after both 1 and 2 weeks, in contrast with flurazepam, which was superior to placebo only after 1 week. Others have noted a significant improvement in sleep onset latency with both drugs relative to placebo. Sleep duration was also greater for both actively treated groups of patients, compared with placebo.[34]

In a double-blind study of 60 patients, the hypnosedative efficacy of zopiclone at dosages of 7.5 or 11.25 mg/day was similar to that of flurazepam 30 mg/day.[35] Both drugs significantly improved sleep onset, sleep soundness and quality of sleep, compared with measurements in the same patients after a 1-night baseline placebo washout.

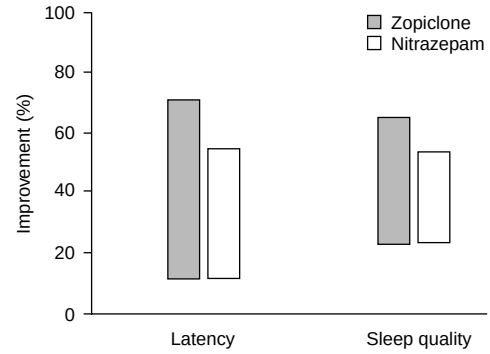

Fig. 2. Range of improvement noted in sleep parameters in patients receiving zopiclone 7.5 mg/day or nitrazepam 7.5 mg/day.[32,36-38]

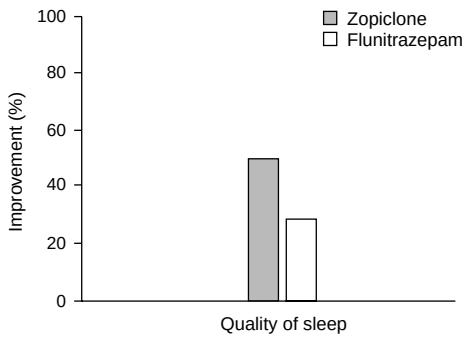

Fig. 3. Range of improvement noted in quality of sleep in patients receiving zopiclone 7.5 mg/day or flunitrazepam 1 to 2 mg/day.[39,40]

The improvements from baseline in these parameters were somewhat greater for flurazepam (85 to 103%) compared with zopiclone (70 to 76%), but were sustained over at least 3 weeks with both therapies.

Results from several clinical studies show that flurazepam 30 mg/day appears to cause more daytime sedation than zopiclone 7.5 mg/day.[26,33-35]

1.1.2 Nitrazepam

Nitrazepam was one of the first benzodiazepines to be directly compared with zopiclone in insomnia, and the efficacy of these agents has now been studied in a number of comparative trials (fig. 2).

Zopiclone 7.5 mg/day was found to induce sleep significantly more rapidly than nitrazepam 5 mg/day, in both crossover ($p < 0.001$) and parallel-group ($p < 0.05$) studies.[32,36]

Two further trials also compared the efficacy of these agents at the same dosages.[37,38] After 6 weeks of treatment, the proportion of patients who received zopiclone 7.5 mg/day and nitrazepam 5 mg/day with prolonged latency was 38 and 44%, respectively; the proportion with >2 awakenings nightly was 18 and 24%, respectively.[38] There were no significant differences between the 2 groups in quality and duration of sleep after 6 weeks, and the physicians' global evaluation of efficacy was similar for both treatments.

In a large, placebo-controlled comparison of zopiclone 7.5 mg/day and nitrazepam 5 mg/day, both active agents were significantly superior to placebo, as measured by the patients' assessment of sleep onset latency, sleep quality and early waking (50 to 60% benefit over placebo in the first week, and 30 to 50% in the second week; $p \leq 0.03$).[37] While physicians' assessments of global efficacy were similar, zopiclone-treated patients reported themselves to be significantly more wide-awake in the morning than those receiving either placebo or nitrazepam ($p = 0.02$).

Results from 2 clinical studies have suggested that daytime sedation and a decrease in the quality of morning awakening are more likely with nitrazepam 5 mg/day than with zopiclone 7.5 mg/day.[32,36,37]

1.2 Medium- and Short-Acting Benzodiazepines

1.2.1 Flunitrazepam

Zopiclone has demonstrated efficacy equivalent to that of flunitrazepam and in some cases greater (fig. 3).

The largest comparative study of zopiclone 7.5 mg/day and flunitrazepam 1 mg/day was a randomised, double-blind trial in 1507 outpatients with insomnia, treated by general practitioners.[39,41] Efficacy was assessed by the total response rate, which quantified sleep quality (covering latency, sleep duration and nocturnal awakenings), feeling of freshness on waking and daytime impairment. Zopiclone was significantly more effective than placebo, with a total response rate of 37.4 *vs* 26.8% ($p = 0.0017$). In contrast, the total response rate in the flunitrazepam group was 30%, which was not significantly different from placebo.

In a 5-day study of depressed patients with insomnia, zopiclone 7.5 mg/day and flunitrazepam 2 mg/day had similar efficacy for most sleep variables, with both drugs having greater improvement from baseline than with placebo.[40] With this increased benzodiazepine dosage, patients' subjective estimates of overall efficacy were higher than for zopiclone (77.4 *vs* 64.4%; $p = 0.04$). However,

the investigators' global assessment of efficacy for both drugs was similar (rated as 'Excellent/Good' for 42% of zopiclone and 38% of flunitrazepam patients). There were improvements in patients' mood on awakening with both drugs, but improvement in vigilance was significant only with zopiclone therapy ($p = 0.006$).

Daytime well-being is a particularly important factor socially, and is also improved following zopiclone therapy. For example, in a large general practice trial, significantly more patients taking zopiclone 7.5 mg/day for 4 weeks had improved daytime well-being than those who took placebo. There was no corresponding benefit with flunitrazepam 1 mg/day.[39,41]

1.2.2 Temazepam

Zopiclone has shown hypnotic efficacy similar to that of the intermediate-acting benzodiazepine temazepam (fig. 4).[42,43] In 1 double-blind, placebo-controlled study, both agents significantly increased sleep duration relative to baseline, although the increase was greater for zopiclone recipients.[42] Significant improvements in sleep latency were noted with both drugs after 1 week of therapy, but only with zopiclone after 2 weeks.

Zopiclone 7.5 mg/day and temazepam 20 mg/day appeared to show similar effects on daytime behaviour.[26,43,44]

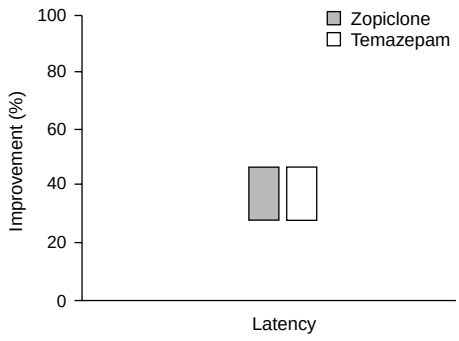

Fig. 4. Range of improvement noted in latency of sleep onset in patients receiving zopiclone 7.5 mg/day or temazepam 20 mg/day.[42,43]

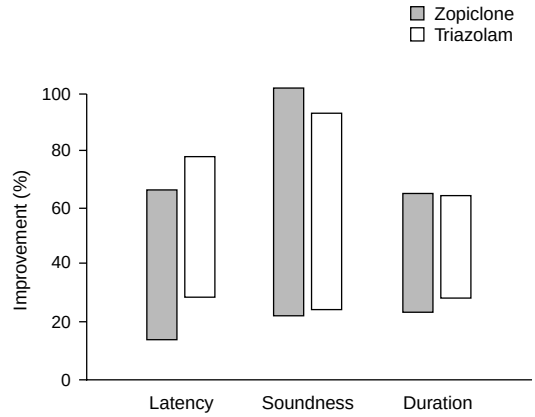

Fig. 5. Range of improvement noted in sleep parameters in patients receiving zopiclone 5 to 7.5 mg/day or triazolam 0.125 to 0.25 mg/day.[45-48]

1.2.3 Triazolam

A number of studies suggest that zopiclone and triazolam have similar efficacy when assessed by a range of sleep parameters in patients with insomnia (fig. 5).

However, other data suggest superior efficacy for zopiclone. Thus, in the large general practice study by Hajak et al.,[39.41] which compared efficacy between zopiclone 7.5 mg/day and triazolam 0.5 mg/day, the total response rate in the zopiclone group was 37.4%, compared with 32.2% for triazolam. While the zopiclone group registered a 40% improvement in total response rate over placebo ($p = 0.0017$), triazolam therapy was only 20% more effective (difference *vs* placebo not statistically significant).

Furthermore, Fontaine and co-workers[49] found that zopiclone 7.5 mg/day was significantly superior to placebo for sleep latency, sleep induction cluster and soundness of sleep, whereas triazolam 0.5 mg/day showed no significant benefit over placebo for the latter 2 parameters.

Zopiclone 7.5 mg/day was also significantly more effective than triazolam 0.5 mg/day according to several efficacy indicators in a large double-blind crossover study.[50] Improvements from baseline for 5 of the 7 items of the Spiegel Sleep Questionnaire were significantly greater in the

zopiclone group than in the triazolam group. Apart from dreams (which were relatively unaffected by either drug), the magnitude of improvement from baseline across all items ranged from 62 to 90% with zopiclone and from 47 to 63% with triazolam.

Results of a large general practice study showed that zopiclone 7.5 mg/day was associated with better daytime well-being than placebo, but there was no difference in daytime well-being between triazolam 0.25 mg/day and placebo.[39,41]

1.2.4 Midazolam

In a 1-week double-blind study of 51 patients, zopiclone 7.5 mg/day produced statistically significant improvements from baseline (no placebo) for all 10 items of the Leeds Sleep Evaluation Questionnaire (LSEQ), whereas the short-acting benzodiazepine midazolam 15mg produced significant improvement for only 6 items.[51] Nevertheless, there were no significant between-group differences in any of the individual LSEQ factors. However, although both agents were considered to be effective hypnosedatives in this study, based on within-group comparisons, zopiclone appeared to be more beneficial especially in the period after awakening.

1.2.5 Lormetazepam and Brotizolam

To our knowledge to date, there has been no direct comparison in patients with insomnia of the efficacy of zopiclone with the frequently used medium-acting benzodiazepines lormetazepam and brotizolam.

1.3 Short- to Medium-Acting Nonbenzodiazepine Hypnosedatives

1.3.1 Zolpidem

Zolpidem is an imidazopyridine that has been shown to have good efficacy that is broadly similar to a number of benzodiazepines, decreasing sleep

Table I. Comparative efficacy of zopiclone (Z) 7.5 mg/day. Relative efficacy of a number of hypnosedatives in the reduction of sleep latency

Reference	Study design	Comparative treatment (daily doses)	Number of evaluable patients	Study period	Latency	Significance level
Quadens et al.[55]	co, pw, db	Flurazepam 30mg	12	13 nights	Z = Fluraz	NS
Elie et al.[33]	pc, pg	Flurazepam 30mg	36	4 wks	Z > Pl	p<0.05
Ponciano et al.[34]	pc, pg	Flurazepam 30mg	24	3 wks	Z > Pl;	p=0.02
					Z = Fluraz	NS
Jovanovic & Dreyfus[56]	db, pg, pw, r	Nitrazepam 5mg	5	14 nights	Z > Nitraz	p<0.08
Agnoli et al.[36]	co	Nitrazepam 5mg	20	2 × 2 wks	Z > Nitraz	p<0.001
Tamminen & Hansen[38]	pg	Nitrazepam 5mg	94	6 wks	Z = Nitraz	NS
Ngen & Hassan[42]	pc, pg	Temazepam 20mg	44	14 days	Z > Pl	p<0.05
van der Kleijn[43]	pc, co	Temazepam 20mg	53	2 × 5 days	Z > Pl	p<0.001;
					Z = Temaz	NS
Mouret et al.[31]	db, r	Triazolam 0.25mg	10	15 nights	Z = Triaz (days 1-3)	NS
					Z < Triaz (days 13-15)	p<0.05
Autret et al.[50]	co	Triazolam 0.5mg	113	2 × 1wk	Z > Triaz	p<0.01
Tiberge et al.[57]	db, r	Triazolam 0.5mg	12	6 nights	Z > Triaz	p<0.05
Fontaine et al.[49]	pc, pg	Triazolam 0.5mg	75	4 wks	Z > Pl; Z = Triaz	p < 0.05; NS
Hayoun & Bagot[47]	pg	Triazolam 0.25mg	127	3 wks	Z = Triaz	NS
van Moffaert et al.[40]	pg	Flunitrazolam 2mg	76	5 days	Z = Flunitraz	NS

co = crossover; **db** = double-blind; **Fluraz** = flurazepam; **Flunitraz** = flunitrazolam; **Nitraz** = nitrazepam; **NS** = no significant difference; **pc** = placebo-controlled; **pg** = parallel group; **Pl** = placebo; **pw** = placebo washout; **r** = randomised; **Temaz** = temazepam; **Triaz** = triazolam; **>, < or =** indicate more effective, less effective or similarly effective (except in final column).

latency and increasing sleep time without a significant rebound effect.[22,52-54] To date, there has been no direct clinical comparison between zolpidem and zopiclone.

A summary of 1 measure of the relative efficacy of zopiclone compared with a number of benzodiazepine hypnosedatives, latency of sleep, is presented in table I.

2. Safety of Zopiclone Use

2.1 Potential for Rebound Insomnia

Withdrawal of hypnosedatives can lead to a worsening of insomnia for a number of days thereafter. The term rebound insomnia is generally restricted to a decrease in sleep duration to a level worse than that before the initiation of therapy. This may also be accompanied by increased frequency of nocturnal awakening and prolonged latency of onset.[58-60] Trials that can detect rebound insomnia therefore generally require a pretreatment baseline, a treatment phase and a withdrawal phase.

A large number of clinical trials of zopiclone withdrawal have been conducted and have found no evidence of significant rebound insomnia.[33,34,37,39,41,45,48,61-63] While some increase in total sleep time was noted in group of 5 patients after withdrawing zopiclone therapy,[31] only 1 case of rebound insomnia was reported in a study of 2542 patients who received zopiclone 7.5 mg/day for up to 28 days.[64] It is possible that the lower incidence of withdrawal effects with zopiclone than with benzodiazepines may be partially due to the effects of zopiclone on sleep architecture: zopiclone delays the onset of rapid eye movement sleep without consistently affecting its duration, and does not decrease time spent in slow wave sleep.[26,65]

Although Fleming et al.[46] noted some rebound insomnia after withdrawal of zopiclone or triazolam, this was worse after triazolam than after zopiclone. Triazolam recipients had a 26 to 36% deterioration in sleep induction, sleep duration and sleep soundness on the first day after drug withdrawal compared with baseline ($p < 0.05$). In contrast, the only significant sleep rebound effect in zopiclone recipients was sleep soundness, which deteriorated by 20 to 28% ($p < 0.05$).

Bianchi and Musch[66] reviewed 25 studies of zopiclone 7.5 mg/day involving a total of 783 patients and 49 healthy volunteers. They found no evidence of rebound insomnia following zopiclone discontinuation, and no adverse changes in sleep latency or duration, or the number of nightly awakenings. Only 1 of these 25 studies reported any evidence of clinically significant rebound with zopiclone.[51] In contrast to zopiclone, rebound phenomena were evident after withdrawal of flurazepam, nitrazepam and triazolam.[66]

Data from numerous sources therefore indicate that rebound effects due to zopiclone withdrawal are considerably less frequent than with benzodiazepines, and need not interfere with clinical benefit. Where they do occur, they generally ameliorate after 1 or 2 days following withdrawal. This is a significant benefit of zopiclone, as avoidance of rebound effects may be one of the major causes of drug dependence.[67] In fact, in a randomised, double-blind, parallel group, multicentre study in private practice, Hajak and colleagues[68] found that the proportion of patients with rebound (rebound rate) was actually higher in the placebo group than in patients receiving active hypnosedatives ($p \leq 0.001$). The rates of rebound that affected sleep quality were lower with zopiclone 7.5 mg/day than with placebo ($p \leq 0.001$). Rebound rates were also lower with zopiclone than with triazolam 0.25 mg/day ($p \leq 0.001$). Thus, pill discontinuation in itself can cause rebound insomnia that worsens sleep and daytime well-being.

2.2 Dependence and Withdrawal Reactions

The substantial data accumulated to date indicate that the risk of withdrawal reactions (commonly including headache, anxiety or nervousness) and dependence with therapeutic doses of zopiclone is very low. Inman et al.[69] studied 13 177 patients who received zopiclone during a prescription-event

monitoring (PEM) study. Of these patients, 85% were prescribed 1 tablet a day, and 11% were prescribed 2 tablets a day. Although it should be remembered that such data are necessarily from patients with varied clinical characteristics and treatment history, no withdrawal reactions were observed after discontinuing the normal 7.5mg therapeutic dose. There were only 7 patients (0.05%) with possible dependence after discontinuing zopiclone: 3 of these patients had taken 6 to 30 tablets daily (45 to 225 mg/day) and none of the 7 patients were confirmed as dependent on zopiclone.

In a pooled analysis of 25 studies of patients taking hypnosedatives for 7 to 28 days, withdrawal symptoms were reported in only 12 out of 441 (2.7%) patients withdrawing from zopiclone (3.75 to 15 mg/day).[66] This rate is below that seen for flurazepam, flunitrazepam or triazolam. A comparison of data from over 700 patients with insomnia receiving zopiclone (3.75 to 15 mg/day) or the benzodiazepines flurazepam (15 or 30 mg/day), flunitrazepam (1 or 2 mg/day) or triazolam (0.125, 0.25 or 0.5 mg/day) indicated that zopiclone is associated with the lowest incidence of withdrawal symptoms of these 4 agents (fig. 6). Thus, overall withdrawal symptoms appear to be infrequent in zopiclone-treated patients and are less common than with some other benzodiazepines. Indeed, zopiclone has proved useful in helping patients withdraw from long term use of other hypnosedatives.[70,71]

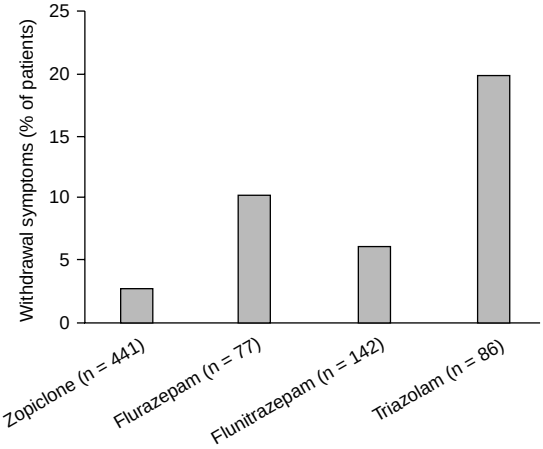

Fig. 6. Pooled incidence of withdrawal symptoms reported from 25 studies after stopping insomnia treatment with the indicated hypnotic agents.[66]

While a number of cases of patients with zopiclone dependence have been reported, nearly all of these were in patients taking high doses of the drug or patients who had a history of drug abuse. The prescribing recommendation for zopiclone is one 7.5mg tablet daily (3.75mg initially in the elderly); this dosage should not be exceeded, and zopiclone should be taken for a maximum of 4 weeks. Where patient compliance differs markedly from this dosage, some dependence has been observed. For instance, Thakore and Dinan[72] reported dependence in a depressed patient taking zopiclone 7.5mg 5 to 6 times per day in an attempt to ease feelings of anxiety and agoraphobia. Four individuals recently reported to have dependence had all increased their dosage considerably from the prescribed 7.5mg daily, in some cases to 30 mg/day.[73] Withdrawal symptoms included anxiety, craving and rebound insomnia. Two other groups have reported a total of 9 patients with zopiclone dependence, all of whom were drug abusers taking as much as 380 mg/day.[74,75] Three further patients who were prescribed zopiclone had a history of schizophrenia or depression, and had increased their doses themselves to relieve symptoms of anxiety.[76] In order to prevent iatrogenic misuse when prescribing zopiclone, it is therefore important to consider the potential for abuse, especially in patients with a history of addiction or psychiatric illness.[77]

One randomised double-blind study assessed the effects of gradual withdrawal of zopiclone 7.5 mg/day (n = 201) after at least 3 months' previous treatment.[78] Patients were randomised to either gradually decrease their dosage over 3 weeks or to continue receiving treatment. The incidence of treatment-related adverse events in the withdrawal and continuation groups was 28 and 20%, respectively. However, it was not possible to ascertain

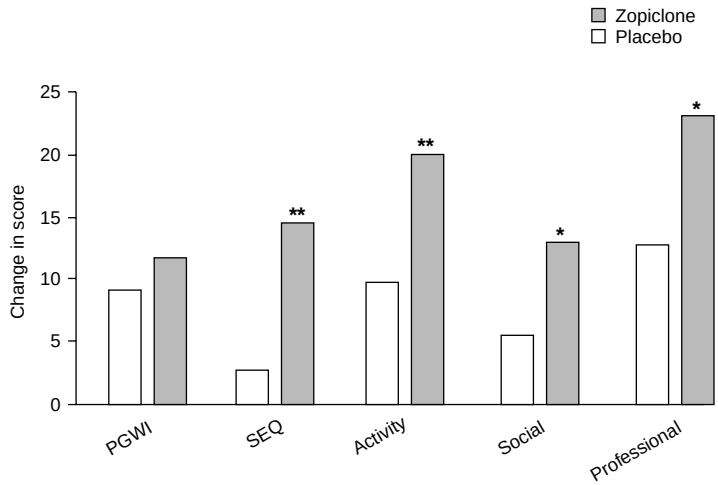

Fig. 7. Improvement in patients' assessment of their well-being after treatment for 14 days with zopiclone 7.5 mg/day or placebo. * $p < 0.01$; ** $p < 0.001$, relative to respective placebo. Scores are obtained from the Psychological Well-Being Index (PGWI), the Sleep Evaluation Questionnaire (SEQ) and other instruments assessing daytime functioning.[79]

whether these events were due to withdrawal or a relapse of the underlying insomnia.

Overall, therefore, the few reports to date of either dependence or other withdrawal effects with standard zopiclone therapy suggest that this agent is associated with very low risk of such events.

2.3 Residual Effects

The incidence of other residual effects with zopiclone use is also low. For example, in a double-blind comparative study of 1291 patients, the proportion of patients reporting daytime well-being (awaking feeling fresh, with no daytime impairment due to tiredness or anxiety) after 14 days treatment was 42% with zopiclone therapy, compared with 37, 33 and 29% after treatment with triazolam, flunitrazepam and placebo, respectively.[39,41] Similarly, a comparison of scores from quality of life instruments measuring daytime function in a number of spheres, including social and professional life, indicated that zopiclone produced a significant improvement in patients' assessment of their well-being (fig. 7). A review of 16 studies assessing psychomotor performance assessed found few reports of residual effects after zopiclone use, with the majority of those that were observed being of small magnitude and rarely persisting beyond 12 hours.[80] One cross-over study also found that driving performance with zopiclone 7.5 mg/day was not impaired in the latter part of the morning, and impairment during the early morning was 5-fold lower than with flunitrazepam 1 mg/day.[81] Studies suggest that the effects of zopiclone on memory are less marked with zopiclone 7.5 mg/day than with flunitrazepam 2 mg/day,

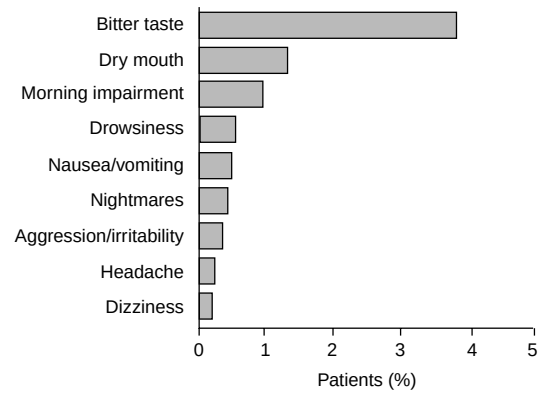

Fig. 8. Pooled incidence of adverse events reported in 3 open-label, post-marketing analyses involving 31 263 patients receiving zopiclone for insomnia.[16,84,85]

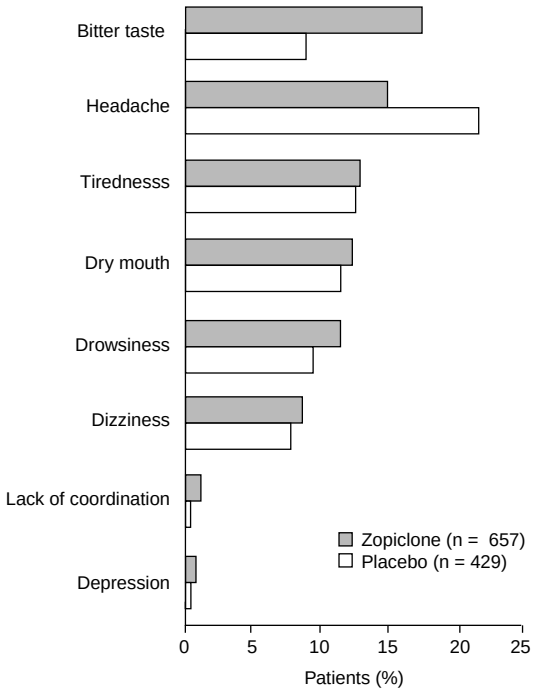

Fig. 9. Pooled incidence of adverse events reported in controlled clinical trials of patients receiving zopiclone (n = 657) or placebo (n = 429) for insomnia.[86]

nitrazepam 5 mg/day, zolpidem 15 mg/day and diazepam 15 mg/day.[82,83]

2.4 Tolerability

As indicated by data from individual clinical trials, pooled analyses and post-marketing surveillance, zopiclone is well tolerated, and its associated incidence of adverse events is low. In the largest available PEM analysis to date, performed in France, only 9.5% of 20 513 patients experienced an adverse event.[84] The most frequent adverse event was bitter taste, which occurred in 3.6% of patients. In 4 smaller post-marketing studies, adverse events occurred in 9.9 to 20.9% of zopiclone-treated patients; bitter taste was again the most frequent, and occurred in 5.0 to 11.6% of patients.

Pooling of results from the French PEM study with 2 further large open-label analyses provided spontaneously reported adverse event data from a total of 31 263 patients, and confirmed the excellent tolerability of zopiclone.[16,84,85] When weighted for the number of patients in each study, the mean incidence of bitter taste was 3.78%; the mean incidence for all other individual events was about 1% (fig. 8).

Adverse event incidences in clinical trials of zopiclone were higher than in post-marketing studies; this would be expected, given the solicited nature of the data. Pooled results from over 1000 patients in clinical trials indicate that, with the exception of bitter taste, the tolerability profile of zopiclone is similar to that of placebo (fig. 9). Bitter taste was reported by <10% of zopiclone recipients.

Reports of fatalities resulting from short term use of zopiclone are very rare. However, Inman et al.[69] obtained British PEM data for the majority of fatalities recorded in a population of 13 177 zopiclone recipients. The distribution of causes of death was very similar to that seen in most PEM studies (table II), and is consistent with the age of the patient population (mean age 54; 22% ≥70 years old). Others have occasionally reported death following deliberate zopiclone overdose.[87,88] However, it is notable that of 20 attempted zopiclone overdoses in the British PEM, including 1 patient who ingested 30 tablets (225mg), none was fatal.[69]

3. Conclusions

The data presented indicate that zopiclone is an established, effective and well-tolerated hynoseda-

Table II. All causes of death of patients reported in a prescription-event monitoring study of 13 177 patients (mean age 55 years) who received at least 1 tablet of zopiclone 7.5mg; 60% of patients were receiving co-prescribed drugs[69]

Cause of death	Total (%)
Psychiatric	27 (5.8)
Nervous system	9 (1.9)
Cardiovascular system	132 (28.6)
Respiratory	43 (9.3)
Cancer	193 (41.8)
Other	22 (4.8)
No details available	36 (7.8)
Total	**462 (100)**

Table III. Summary of relative estimates of zopiclone efficacy and safety[a]

Hypnosedative	Efficacy	Potential for rebound insomnia	Potential for dependence	Withdrawal reactions	Tolerability	Daytime well-being
Zopiclone	+++	+	+	+	+++	+++
Long-acting benzodiazepines	++/+++	+	++	+	+	+
Medium/short-acting benzodiazepines	++/+++	+++	+++	++	+	++

a Properties of individual benzodiazepines can vary markedly with the drug and dosage.

+ = low; **++** = intermediate; **+++** = high.

tive. Zopiclone, a nonbenzodiazepine cyclopyrrolone, has at least similar efficacy to the majority of benzodiazepines, and results in comparable improvements in the latency of onset, quality and duration of sleep.

In over 15 years of clinical usage of zopiclone, the benefits associated with its use appear to far outweigh the risks, notably those of withdrawal or dependence. Results from a large number of studies indicate that rebound insomnia after withdrawal of zopiclone is possible but infrequent.[89] This contrast with most benzodiazepines, with which as many as one-third of long term users may experience a withdrawal syndrome, even after tapered withdrawal.[90] The low incidence of rebound insomnia with zopiclone highlights its superiority over benzodiazepines, as this property may be a factor in encouraging long term dependence.

Similarly, in contrast to the well known and established risks with benzodiazepines, the available clinical data on dependence on zopiclone are positive. When used in accordance with the prescribed regimen, not exceeding 4 weeks' therapy, there have been very few reports of dependence with zopiclone: the few that do exist have nearly all been in individuals who were abusing the drug (so care should be exercised when treating vulnerable patients). Compared with other agents in this class, therefore, zopiclone is a relatively well tolerated agent, with dependence on long term use occurring only rarely.[89]

These properties combine to class zopiclone as one of the most highly recommended agents for insomnia management.[91] Indeed, in a European pharmacoeconomic analysis using the System of Objectified Judgement Analysis, zopiclone was rated as one of the leading candidates for formulary inclusion, while nitrazepam, loprazolam and flunitrazepam were not recommended.[92]

There is now over 15 years of clinical evidence supporting the efficacy and superior safety profile of zopiclone in insomnia (table III). During this period, over 2.5 billion zopiclone units have been dispensed in over 30 countries. Evaluation of the accumulated evidence consistently indicates that overall zopiclone is a clinically superior alternative to the majority of benzodiazepines for the short term pharmacological treatment of insomnia.

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