REVIEW ARTICLE

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Comparative Tolerability of Newer Agents for Insomnia

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Contents

Abstract

Newer treatment options for insomnia include the non-benzodiazepine hypnotics zolpidem, zolpidem-controlled release, zaleplon, zopiclone, eszopiclone and the melatonin receptor agonist, ramelteon. These compounds are generally well tolerated and present favourable safety profiles in comparison with the older benzodiazepines and barbiturates. Commonly cited impairments of memory formation and decrements in psychomotor performance are related to the mechanism of action of hypnotics, and are both dose- and time-dependent. These effects typically are minimal on the morning following night-time administration. The non-benzodiazepines are associated with some risk for dependence and abuse. However, concerns regarding such risks appear to be greater than warranted by empirical evidence. The appropriate therapeutic use of hypnotics is generally not associated with physiological responses that are commonly thought to lead to dependence, such as tolerance or discontinuation effects. Former substance abusers and psychiatric patients appear to be at greatest risk. The labelling of hypnotics was recently updated to incorporate warnings about very rare, but serious adverse events that have been identified in postmarketing surveillance. These events include anaphylaxis (severe allergic reaction); angio-oedema (severe facial swelling); and complex sleep-related behaviours, which may include sleep-driving, making phone calls and preparing and eating food. This article will review the adverse event profiles of these newer sedative hypnotics, their effects on memory and psychomotor performance, abuse liability concerns and the most recent information about the rare adverse effects that prompted the recent revision to the labelling of drugs in the hypnotic class.

The number of pharmacological treatment options for insomnia has greatly expanded in recent years. Zopiclone became the first non-benzodiazepine hypnotic to be approved in the European market in 1986. In 1992, zolpidem became the first hypnotic in this class to be approved by the US FDA. It was followed soon after by zaleplon in 1999 and eszopiclone, the *S*- (+) isomer of zopiclone, in 2004. Both zolpidem-controlled release (CR), an extended release formulation of zolpidem, and ramelteon, the first melatonin receptor agonist, were approved in 2005. Other compounds are in varying stages of development, with many employing similar mechanisms of action to these agents (i.e. GABA receptor agonists or melatonin receptor agonists), novel mechanisms or novel formulations.

Prior to the availability of newer hypnotics, clinicians were limited to the use of benzodiazepines and the older, and considerably less safe, barbiturates. The newer non-benzodiazepines and the melatonin receptor agonist appear to offer several advantages over the older compounds with regard to efficacy and safety, but still have the potential to result in clinically significant adverse events (AEs).

This article will review the AE profiles of these newer sedative hypnotics, their effects on memory and psychomotor performance, abuse liability concerns and the most recent information about rare adverse effects, which prompted a recent revision to the labelling of drugs in the hypnotic class. Literature searches employing the name of each drug reviewed here as key words were conducted through December 2008 using the MEDLINE database administered by the National Library of Medicine and the National Institutes of Health.

1. Adverse Event Profiles

During its clinical development programme, zolpidem was primarily evaluated in studies lasting up to 4 or 5 weeks.[1-10] AEs that occurred at statistically higher rates than in the placebo-treated populations included drowsiness (2% of zolpidem-treated patients), dizziness (1%) and diarrhoea (1%).[11] Dizziness, 'drugged feeling', lethargy and drowsiness were the most commonly observed AEs associated with zolpidem treatment in longer studies lasting from 28–35 nights.[11] Treatment-emergent AEs associated with zolpidem that led to subject discontinuation included drowsiness, dizziness, headache, nausea, vomiting, amnesia and falls.[11] During a 4-week outpatient surveillance study of zolpidem, 118 of almost 17 000 patients discontinued because of an AE.[12] Discontinuations were attributed to nausea (36), dizziness (35), malaise (23), nightmares (20), agitation (19) and headache (18).

The AE profile of zolpidem-CR was similar to that of its original formulation. During treatment, lasting up to 3 weeks, the most commonly observed AE reactions associated with treatment were headache, next-day somnolence and dizziness.[13] In a 6-month trial, the same AEs seen during short-term therapy were noted along with a higher incidence of anxiety.[14] AEs most commonly associated with treatment discontinuation in the clinical development programme included somnolence, anxiety and depression. Table I presents AEs reported during a 3-week zolpidem-CR study.[13]

In a pool of three zaleplon studies that lasted between 28 and 35 nights, the most common treatment-emergent AEs were amnesia, paresthesia, abdominal pain, somnolence, eye pain, dysmenorrhoea, dizziness and headache (see table II).[15,16] No zaleplon-related AEs led to study discontinuation at a rate of ≥1%.

A postmarketing surveillance study of over 20 000 insomnia patients who used zopiclone found that the most common AEs were bitter taste (3.6%), dry mouth (1.6%), difficulty arising in the morning (1.3%), sleepiness (0.5%), nausea (0.5%) and nightmares (0.5%).[17]

Table I. Adverse events (AEs) during a zolpidem-controlled release (CR) 3-week, double-blind, placebo-controlled study[11]

AE	Placebo (%) [n = 100]	Zolpidem-CR (%) [n = 102]
Headache	16	19
Somnolence	2	15
Dizziness	5	12
Nausea	4	7

Table II. Incidence of treatment-emergent adverse events (AEs) in long term (28 and 35 nights), placebo-controlled clinical trials of zaleplon[11,15,16]

AE	Placebo (%) [n = 344]	Zaleplon 5 or 10 mg (%) [n = 569]	Zaleplon 20 mg (%) [n = 297]
Abdominal pain	3	6	6
Headache	35	30	42
Asthenia	5	5	7
Nausea	7	6	8
Dizziness	7	7	9
Somnolence	4	5	6

In two eszopiclone clinical trials lasting up to 6 weeks, one in adults and one in the elderly, the most common treatment-emergent AEs were unpleasant taste, somnolence, dizziness, hallucinations, headache, dry mouth, vomiting, anxiety, confusion, depression, abnormal dreams, rash and neuralgia.[18,19] In both of these studies, no event that resulted in discontinuation occurred at a rate >2%. AEs reported during a 6-week study are shown in table III.[18]

Somnolence, fatigue and dizziness were the most common treatment-related AEs observed in phase I–III studies of ramelteon.[21-24] The most frequent AEs that led to discontinuation in subjects treated with ramelteon were somnolence, dizziness, nausea, fatigue, headache and insomnia. AEs reported during a 5-week ramelteon trial are shown in table IV.[21]

2. Memory Effects

The impact of hypnotics on memory appears to be dependent upon the mechanism of action of the drug, dose and the time interval between dosing and assessment. Generally speaking, the impact on memory is minor when testing is performed 8 or more hours after dosing. Evaluations performed closer to the time of dosing produce more mixed results.

Zolpidem does not appear to impact retrograde memory, i.e. recall of material presented prior to hypnotic administration.[25] However, two articles indicate that anterograde memory impairment (i.e. recall of material presented after hypnotic administration) has been seen at doses of 10 and 20 mg.[8,25] These results contrast with most other studies of nocturnal administration, which have found little effect on either type of memory formation.[26-33] Daytime administration studies have produced evidence of dose- and time-related impairment of learning and recall, with the greatest impact typically observed at or near peak plasma concentrations.[26,34-41]

There are few published reports of the effects of zolpidem-CR on next-day memory and those that exist involve healthy volunteers.[42,43] In the absence of clinical evidence, the most informative data regarding the effects of zolpidem-CR may be those obtained from pharmacodynamic studies comparing immediate-release zolpidem to zolpidem-CR.[44] These data suggest that zolpidem-CR's longer half-life may extend the period of time after administration that anterograde memory impairment might be observed.

Daytime administration of zaleplon has produced mixed results on memory formation, with some evaluations indicating no impairment in memory formation[27] and others finding time-related effects.[45] Bedtime administration of zaleplon has consistently been shown to have no impact on next-day memory performance.[41,46]

Daytime administration studies have shown zopiclone produces time-related impairment of memory formation, with the greatest impairment seen near peak plasma concentrations.[47-49]

Table III. Treatment-emergent adverse events (AEs) during a 6-week, double-blind study with eszopiclone[20]

AE	Placebo (%) [n = 99]	Eszopiclone 2 mg (%) [n = 104]	Eszopiclone 3 mg (%) [n = 105]
Anxiety	0	3	1
Confusion	0	0	3
Depression	0	4	1
Nervousness	3	5	0
Hallucination	0	1	3
Dizziness	4	5	7
Dry mouth	3	5	7
Headache	13	21	17
Somnolence	3	10	8
Unpleasant taste	3	17	34

Table IV. Adverse events (AEs) during a 5-week, double-blind, placebo-controlled study with ramelteon (reproduced from Zammit et al.,[21] with permission from the American Academy of Sleep Medicine)

AE	Placebo (%) [n = 131]	Ramelteon 8 mg (%) [n = 139]	Ramelteon 16 mg (%) [n = 135]
Headache NOS	18.3	19.4	17.8
Somnolence	1.5	7.9	7.4
Fatigue	2.3	9.4	4.4
Nausea	2.3	4.3	4.4
Nasopharyngitis	3.1	2.9	3.7
Diarrhoea NOS	1.5	1.4	3.7
URI NOS	3.1	4.3	0.7
Dizziness	3.8	3.6	1.5
Nasal congestion	0.8	1.4	3.0

NOS = not otherwise specified; **URI** = upper respiratory tract infection.

Studies involving bedtime administration of zopiclone 7.5 mg have found evidence of memory impairment up to 10 hours post-dose.[50,51]

The eszopiclone clinical development programme has produced few published data on its memory effects.[52,53] Instead the FDA and other regulatory agencies have relied on data obtained for zopiclone, its parent compound, for insight into its properties in this area.[54]

The effect ramelteon has on memory has been evaluated in two published 2-night studies. Both employed immediate and delayed-memory assessments on the morning after drug administration. Neither found any decrements in performance relative to placebo values.[22,24]

3. Psychomotor Performance

Commonly used pharmacodynamic tools for the assessment of next-day residual effects attributable to hypnotics include the digit symbol substitution test (DSST), symbol copying test, critical flicker fusion (CFF), choice reaction time (CRT), compensatory tracking test (CTT) and Rey auditory verbal learning test (RAVLT) tests.

The zolpidem label makes note of a small, but significant, impact on DSST scores in three studies in adults and one study in the elderly.[11] However, most published clinical trials have not found a significant impact on any pharmacodynamic assessment.[10,29,55-62] Daytime studies of zolpidem suggest that psychomotor effects are time- and dose-dependent. Zolpidem doses of up to 20 mg were shown to impair psychomotor performance from 3 to 6 hours after dosing.[35,36,39,41,63] Importantly, postmarketing surveillance suggests that higher doses in the elderly are significantly correlated with increase fall rates and risk of hip fracture.[64] The impact of zolpidem on driving has been evaluated in multiple studies. Bedtime and middle-of-the-night dosing with zolpidem 10 mg have not been shown to produce any clinically relevant decrements in driving performance, but dosing with 20 mg (both at bedtime and during an experimental awakening) negatively impacted driving ability.[65-67]

The next-day effects of zolpidem-CR were examined in at least three studies. The first found a decrement relative to placebo in one aspect of a psychomotor test (CTT-reaction time), whereas other evaluations and other CTT measures were indistinguishable between active treatment and placebo.[42] The second study involved healthy elderly subjects and found no difference between zolpidem-CR and placebo on a battery of six neuropsychological tests.[43] The third study found no changes relative to baseline values in chronic insomnia patients on either the DSST or RAVLT over a 3-week treatment period.[13]

Bedtime zaleplon administration does not appear to be associated with any decrements in psychomotor performance.[41,68,69] Notably, several studies involving an experimental awakening and middle-of-the-night dosing with zaleplon found no residual psychomotor effects even when the drug was administered as little as 2 hours prior to morning awakening.[35,70,71] Similar to results seen with zolpidem, daytime administration of zaleplon has been shown to produce decrements in psychomotor performance near peak plasma concentrations.[45,72] Driving performance with zaleplon was evaluated in multiple studies of both bedtime administration and administration during an experimental middle-of-the-night awakening. None of these studies found any impairment with either zaleplon 10 or 20 mg

when administered ≥4 hours prior to the driving evaluation.[50,51,67,73]

Assessments of psychomotor performance following zopiclone administration have been mixed. One daytime administration study found decrements in DSST, CFF and CRT 2 hours following administration of zopiclone 7.5 mg; effects were no longer statistically significant at 6 hours post-dose,[74] while another found psychomotor performance decrements relative to placebo at 1 hour post-dose, which disappeared at 4 hours post-dose.[48] One bedtime administration study of zopiclone 7.5 mg found no difference from placebo on psychomotor assessments as early as 5 hours after administration,[75] while another found decrements at 10 hours post-dose.[51] Multiple studies conducted early in the clinical development of zopiclone found no psychomotor-performance decrements after periods up to 6 weeks in outpatient populations.[76-79] Complicating the comparability of these data to more recently obtained study results, these evaluations did not carry out psychomotor evaluation at a fixed timepoint following the previous dose. The impact of zopiclone on driving ability has been assessed in studies employing night-time dosing and dosing during an experimental awakening. Driving performance was shown to be impaired up to 10 hours post-dose.[50,51,73]

The DSST has been used to evaluate the next-day psychomotor effects of eszopiclone in at least three trials. In a study employing a model of transient insomnia, no decrements in DSST performance were noted with active treatment.[80] Similarly, a 6-week study found no DSST impairments relative to either placebo or baseline values at any point in time.[18] Pharmacokinetic studies in healthy adults and elderly subjects found that the impact of eszopiclone on DSST performance peaked within 1–2 hours after administration.[81] DSST scores returned to pre-treatment levels approximately 5 hours after dosing in the adult population and within 2 hours in the elderly subjects. In contrast with the results seen with zopiclone, a study involving bedtime administration of eszopiclone 3 mg found no impairment on next-day driving performance.[52]

The next-day psychomotor effects of ramelteon have been evaluated using the DSST in at least three published studies. These trials found that ramelteon was indistinguishable from placebo at doses up to eight times the approved dose of 8 mg.[22,24,82] There are also two evaluations of the impact of ramelteon on middle-of-the-night balance near peak plasma concentrations. In the first trial, subjects were awakened 1.5–2 hours after study drug administration to perform a balance assessment.[83] Measures of subjects' body sway in the ramelteon and placebo groups were similar, while the active control (zolpidem 10 mg) produced significant changes. A similar protocol was employed in the second study.[84] Consistent with the results from the first trial, no difference was observed between ramelteon and placebo, while the active control (zopiclone) was associated with significant performance decrements.

4. Abuse Liability

There is concern about the potential abuse liability for most drugs indicated for insomnia. These concerns appear to be exaggerated relative to the dearth of evidence suggesting that hypnotics are associated with physiological dependence. However, cases of dependence on both benzodiazepines and non-benzodiazepines are well documented phenomena, especially in individuals with a history of drug abuse or psychiatric illness.

Zolpidem does not appear to be associated with the development of tolerance or dependence when used at therapeutic doses. The lack of tolerance and dependence has repeatedly been established in many trials in both adult patients and in the elderly.[1,2,85-90] Furthermore, one evaluation found that drug-consumption patterns were similar in zolpidem (10 mg) and placebo groups after 4 weeks of treatment, resulting in the investigators' interpretation that drug-seeking behaviour is not induced by zolpidem.[91]

Drug-discrimination studies in healthy adults have shown that zolpidem (15–45 mg) is perceived to be different from benzodiazepines, barbiturates and alcohol.[25,26,92,93] Zolpidem

repeatedly was associated with more negative adverse effects (e.g. vomiting and nausea) than triazolam, and did not increase the 'euphoria' scale of the Addiction Research Center Inventory (ARCI)-Morphine Benzedrine Group.[25,26,92,93]

One postmarketing surveillance report involved a MEDLINE literature review of case reports from 1966 to 2002.[94] This report found similar rates of zolpidem abuse in men and women reporting from all age groups. Most cases involved individuals with drug and alcohol abuse problems and/or psychiatric illness. Even so, the author noted that the incidence of reported dependence is ''remarkably lower than that of benzodiazepines used for the treatment of disturbed sleep''. A second postmarketing surveillance report used information gathered from the Drug Commission of German Physicians and indicated that through March 1999, there were 19 cases of zolpidem dependence, 12 cases of withdrawal and 6 cases of abuse, predominantly in patients with a history of substance abuse.[95] To put this number into context, in 1996 alone, 45.3 million doses of zolpidem 10 mg were prescribed in Germany. The author of this analysis also noted that the relative rate of zolpidem abuse was significantly lower than that seen with benzodiazepines, stating ''the risk of developing [zolpidem] dependence is very small.''

Abrupt treatment discontinuation of zolpidem-CR has been shown to produce a single night of rebound insomnia. In a 3-week comparison of zolpidem-CR and placebo, patients experienced a significant worsening in sleep initiation, duration and maintenance during the first night only of the single-blind placebo run-out period.[13]

Participants in a 6-month study comparing zolpidem-CR with placebo were instructed to take study medication 'as needed' 3–7 nights a week.[96,97] Over this period, sleep was rated using morning questionnaires. Questionnaires from single nights without zolpidem-CR following 4 consecutive treatment nights demonstrated no worsening in subjective sleep maintenance (months 1–6) or duration (months 2–6) parameters. During the 3 nights following permanent treatment discontinuation, no worsening relative to baseline values was observed in these measurements.

Zaleplon does not appear to produce tolerance, and its abrupt discontinuation does not appear to produce rebound insomnia or withdrawal symptoms in adult[15,16,85,98] or elderly insomnia patients[99] over periods of up to 5 weeks long. Patients with a history of drug abuse rated zaleplon as comparable to triazolam on measures of drug-effect and drug liking, suggesting that both drugs possess similar abuse potential.[72] Studies in baboons found that zaleplon can produce physical dependence similar to that of triazolam[100] and that the animals could differentiate between zaleplon and vehicle.[101]

A postmarketing study examining UK data on hypnotic drug abuse found that street purchases of zopiclone and zolpidem were motivated by a similar pattern of use either as sleep aids or to get high.[102] The MEDLINE literature review mentioned earlier[94] found that the abuse potential of zopiclone was similar to that of zolpidem.

A comparison of zopiclone and triazolam in former alcoholics found that triazolam was preferred to zopiclone, but both drugs produce similar results on a profile of mood scales and ARCI subscales measuring the perceived drug effect.[103] These results suggest that zopiclone has a lower potential for abuse than triazolam, although it is far from risk free for former substance abusers.

The eszopiclone label and a review of the abuse potential of hypnotics both rely heavily on data gathered for zopiclone, the parent compound of eszopiclone.[11,54] As a result of the relatively short amount of time that eszopiclone has been available in the US market, there are few published reports of cases of abuse or dependence.[104]

Clinical trials of eszopiclone have found little evidence of the development of tolerance or withdrawal effects. In a 6-week study, sleep improvements generally were maintained following abrupt discontinuation treatment, but the group treated with 2 mg experienced small, but statistically significant, worsening of sleep efficiency and wake time after sleep onset during the first night after treatment was discontinued.[18] No tolerance was observed in either of two 6-month

studies,[105,106] and no rebound insomnia or CNS withdrawal effects were noted during a 2-week, single-blind placebo run-out period.[105] Similarly, no tolerance or withdrawal symptoms following treatment discontinuation were noted during a 12-month eszopiclone open-label study.[107]

Ramelteon is the only compound approved for insomnia therapy that has demonstrated no abuse potential in either pre-clinical animal models or in clinical evaluation in humans.[54] Because of this unique characteristic, it is the only insomnia therapeutic that is not classified as a scheduled drug by the US Drug Enforcement Administration.

Rhesus monkeys have commonly been used to demonstrate the addictive properties of various medications. Experiments designed to test for benzodiazepine agonist-like discriminative stimulus effects in rhesus monkeys found that ramelteon does not possess this property.[108] Treatment with ramelteon for 1 year, with periodic suspensions of treatment to allow for the assessments of discontinuation effects, found no behavioural effects with either active treatment or discontinuation, suggesting that ramelteon is unlikely to produce physical dependence.[109] Finally, a pre-clinical study found that ramelteon produced no positive-reinforcing effects in an intravenous self-administration experiment in rhesus monkeys.[110]

The results from studies in humans are consistent with those seen in the pre-clinical animal studies. Studies involving dosing with ramelteon for up to 5 weeks in adults without a history of substance abuse have found no evidence of withdrawal effects or rebound insomnia.[23,111] Adults with a history of sedative abuse participated in a study of the abuse potential and behavioural effects of ramelteon.[112] At all timepoints and at doses up to 20 times the approved dose strength, ramelteon was similar to placebo on the primary outcome measure of 'drug liking' and was similar to placebo on 'drug strength', 'drug liking', 'good effects' and 'street value' at 24 hours post-dose. In contrast, and consistent with its established abuse potential, the active control (triazolam) showed dose-related effects on all of these measures.

5. Drug-Drug Interactions

Hypnotics have been evaluated in conjunction with other commonly used medications to assess the likelihood of clinically significant drug-drug interactions. All of the hypnotics reviewed here have been shown to produce an additive effect on pharmacodynamic assessments when administered concomitant with ethanol.[11,113-117] These effects were limited to decreases in performances and were not accompanied by any changes in the pharmacokinetic properties of the hypnotic.

Zolpidem, zaleplon, eszopiclone and ramelteon were each co-administered with digoxin, a medication commonly used to treat heart conditions.[11,118-120] No clinically significant changes were observed in the pharmacokinetics of either the hypnotics or digoxin. Similar evaluations were conducted with warfarin, an anticoagulant. Again, no changes were noted in the pharmacokinetics of either warfarin or zolpidem, zaleplon, eszopiclone and ramelteon.[11,25,121,122]

Drug-drug interaction studies have been conducted using medications known to either inhibit or induce cytochrome P450 enzyme (CYP) 3A4 metabolism, which is the pathway that is perhaps most often employed in the metabolism of pharmaceutical products. Co-administration with the CYP3A4 inhibitor ketoconazole has been shown to increase the area under the (plasma/serum) concentration-time curve (AUC) and other pharmacokinetic parameters including maximum concentration (C_{max}) and half-life of zolpidem, eszopiclone and ramelteon.[11,123,124] Other CYP3A4 inhibitors have also been shown to increase exposure to zolpidem (itraconazole[124]) and zaleplon (erythromycin,[11,115] cimetidine[125]). The CYP3A4 inducer rifampin (rifampicin) has been shown to reduce AUC and other pharmacokinetic parameters of co-administered zolpidem, zaleplon, zopiclone and ramelteon.[11,115,126,127]

Hypnotics have been extensively evaluated in co-administration studies with other CNS active pharmaceuticals. Concomitant administration of zolpidem and imipramine produced an additive effect on alertness and decreased the AUC of imipramine.[11,25] Co-administration of zolpidem

and chlorpromazine also produced additive effects on pharmacodynamic performance.[128] Co-administration with sertraline increased zolpidem C_{max} while decreasing time to maximum concentration.[129] Concomitant administration of zaleplon with paroxetine and venlafaxine produced no evidence of interaction.[11] However, co-administration of zaleplon and both thioridazine and imipramine produced decreases in psychodynamic performance without impacting pharmacokinetics while zaleplon and promethazine decreased the maximal plasma concentration of zalpeon without impacting pharmacodynamics.[11,130] Eszopiclone co-administered with either paroxetine or lorazepam produced no drug-drug interactions.[11] Concomitant administration of eszopiclone and olanzapine produced psychomotor performance deficits, but no changes in pharmacokinetics.[11] Ramelteon AUC and C_{max} were both significantly increased when co-administered with either fluvoxamine or fluconazole.[11,123]

6. Rare Events

In December 2006, the FDA requested that the labelling of all drugs approved for the treatment of sleep disorders modify their labels to include warnings about rare, but potentially very serious AEs. These AEs were:

- anaphylaxis (severe allergic reaction) and angio-oedema (severe facial swelling), which can occur as early as the first time the product is taken;
- complex sleep-related behaviours, which may include sleep-driving, making phone calls and preparing and eating food (while asleep).

There was a remarkable spate of reporting in the lay press in 2006 about zolpidem and complex sleep behaviours, which resulted in a predictable increase in concern in the general population. Most of the mentions in the lay press sourced three articles originally published by The New York Times in March 2006: one on sleep eating and one on sleep driving.[131-133] The anecdotal stories referenced here frequently mention concurrent alcohol and zolpidem consumption, and refer to individuals continuing to carry on with normal activity after taking zolpidem instead of immediately going to bed as advised by the label.

In spite of the heightened public attention generated by these articles, there is relatively little published information in the academic press about sleep eating, sleep driving, anaphylaxis or angio-oedema associated with hypnotic usage. A number of individual case studies have been published,[134-140] but the author is unaware of any comprehensive review of this material, which is probably related to the relative rarity of these events. In fact, a 2007 case report describing a patient who experienced sleep eating behaviours while on zolpidem identified only six previously reported cases of sleep eating associated with hypnotic usage in the academic literature.[141]

Several factors must be considered when assessing the significance of reports of complex behaviour following hypnotic use. Such reports commonly are case reports or case series; they do not occur in the context of carefully controlled clinical studies. Therefore, it is important to determine if reports are obtained from people who were prescribed and using hypnotics according to label instructions for appropriate therapeutic purposes versus those using medication that has been diverted for recreational or other illicit use. Furthermore, for each report, it is important to consider the hypnotic dose, time of dosing, time of behaviour relative to dosing and the use of concomitant medication, drugs or alcohol.

Complex behaviours following hypnotic use have primarily been identified as a result of post-marketing surveillance. These behaviours were not identified in the clinical development programmes of hypnotics. Therefore, the actual risk faced by an individual who is taking a therapeutic hypnotic dose as instructed, while apparently low, is not known. In any event, to warrant a modification to the labelling of all hypnotic drugs, it must be inferred that US regulatory authorities perceive these AEs to be extremely serious regardless of their frequency of occurrence.

7. Conclusions

The non-benzodiazepine hypnotics zolpidem, zolpidem-CR, zaleplon, zopiclone and eszopiclone, and the melatonin receptor agonist ramelteon are the newest treatment options for insomnia. These compounds present a relatively low risk for AEs and are generally well tolerated, especially in comparison with older hypnotics. Hypnotics that act at the GABA receptor generally impact memory formation and psychomotor performance, with the greatest effects observed when assessments are executed near the time of peak plasma drug concentration. Most assessments performed on the morning following night-time administration show few residual effects.

Abrupt discontinuation of treatment of some of these compounds may produce a single night of rebound insomnia. Long-term studies indicate sustained therapeutic effects of hypnotics over time; evidence of tolerance is largely absent. Studies in former drug users indicate that several of the non-benzodiazepines can produce effects, which suggest the potential for abuse. However, the number of reports of drug abuse for these compounds appears to be relatively low in comparison with their widespread therapeutic application.

The labelling of hypnotics was recently updated to incorporate warnings about rare but serious AEs, which have been identified in post-marketing surveillance. These events include anaphylaxis (severe allergic reaction), angio-oedema (severe facial swelling) and complex sleep-related behaviours, which may include sleep-driving, making phone calls and preparing and eating food. While the risk of developing such adverse reactions is not known, these events appear to impact only a very small percentage of patients.

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