Managing Dependence and Withdrawal With Newer Hypnotic Medications in the Treatment of Insomnia

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Hypnotic drugs are widely prescribed medications, especially for the elderly. The benzodiazepines and newer, nonbenzodiazepine compounds, such as zopiclone, zolpidem, and zaleplon, are the current favorites. Benzodiazepines can be either long acting (flurazepam and nitrazepam), medium acting (temazepam), or short acting (triazolam). However, duration of action is prolonged in the elderly and is also dose dependent. Although insomnia can be due to many causes, physical and psychiatric disorders are the most common. Many people with insomnia, however, are chronically symptomatic without apparent cause ("primary" insomnia). Long-term use of a prescribed hypnotic is, unfortunately, a common consequence. Upon discontinuation of prolonged hypnotic use, withdrawal syndromes can occur that comprise a characteristic set of symptoms and signs temporarily associated with the discontinuation and not reported prior to treatment. These are generally taken as indications of physical dependence. Of major concern is abuse—the use of high doses for recreational purposes, outside the medical context, and possibly with supplies illegally obtained. Withdrawal is usually uneventful with the newer nonbenzodiazepine drugs. They can even be used as transitional therapies in the more difficult task of discontinuing benzodiazepines in long-term dependent users. However, dosage considerations are important with all hypnotics, and treatment, especially in the elderly, should be at the lowest effective dose and for the shortest duration.

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Hypnotic drugs are commonly prescribed medications. In many countries, the recommended duration of use has become increasingly restrictive with a maximum of 2 to 4 weeks. Nevertheless, many patients take hypnotic medication over a long period of time, reflecting the chronic nature of many insomnia complaints. Unfortunately, discontinuation following continuous use beyond 2 to 4 weeks may be followed by a plethora of symptoms, the most severe constituting a full-blown withdrawal syndrome.[1] This experience may, in turn, lead to resumption of medication with long-term or lifelong reliance on hypnotics. Furthermore, the clinical implications of withdrawal symptoms are not clear, nor are there standard protocols for the management of these situations.

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This review examines withdrawal syndromes and evaluates currently available hypnotics for their propensity for association with these syndromes. The emphasis will be on the newer hypnotics, zopiclone, zolpidem, and zaleplon, rather than on the benzodiazepines. During the past decade, benzodiazepines have been partly superseded by these short-acting compounds. Zopiclone has an elimination half-life averaging 5 hours,[2] zolpidem, about 3 hours,[3] and zaleplon, about 1 hour.[4] All 3 are chemically nonbenzodiazepine in structure; zopiclone is a cyclopyrrolone derivative; zolpidem, an imidazopyridine derivative; and zaleplon, a pyrazolopyrimidine derivative. Although all act on the benzodiazepine γ-aminobutyric acid type A ($GABA_A$)-chloride-ionophore, zopiclone binds atypically, and zolpidem and zaleplon are selective on the benzodiazepine subtype 1 receptor. This selectivity is claimed to confer specific hypnosedative properties. However, compared with zopiclone and zolpidem, zaleplon has a much lower affinity for the benzodiazepine subtype 1 receptor,[5] enabling effective induction of sleep without significant impairment at peak plasma concentrations. Whatever the putative biochemical distinctions between these newer drugs and the benzodiazepines, the question of withdrawal potential needs to be addressed in practical clinical terms.

WITHDRAWAL AND DEPENDENCE

Relapse and rebound, the most thoroughly researched discontinuation phenomena, are discussed elsewhere in this publication. Soldatos et al.[6] recently published a comprehensive, detailed review. Withdrawal syndromes comprise a characteristic set of symptoms and signs temporarily associated with discontinuation of a hypnotic. At least 3 symptoms not previously experienced by the patient should develop. With central nervous system depressants such as the hypnotics, the most typical withdrawal phenomena are perceptual hypersensitivity (photophobia, hyperacusis, hyperalgesia) and systemic symptoms (e.g., anorexia, malaise, and weight loss).[7] The psychological symptoms of insomnia—anxiety, tension, and restlessness—are not well defined and may resemble the original symptom profile. Withdrawal from high-dose (supratherapeutic) levels is the norm and may be severe, with seizures or psychosis. Problems may also be encountered in 10% to 30% of those discontinuing normal-dose protracted (> 6 months) use. Withdrawal is considered evidence of *physical dependence*, and *psychological dependence* is assumed if the individual shows "drug-seeking" behavior (e.g., pestering the doctor for sleeping pills). One type of dependency can exist without the other. *Abuse* refers to the regular or intermittent use of high doses outside the medical context. Although most drugs of dependence are abused, not all abused drugs induce physical dependence.

The methodology for the assessment of rebound in insomnia has been reviewed in detail.[8] Awareness of discontinuation problems has led to various studies during the development of new hypnotics. Many regulatory authorities regard such studies as mandatory. Protocols exist for the assessment of rebound after short-term use and withdrawal after long-term use,[9] which occurs despite the licensing for hypnotics now being restricted to short-term use in many countries. Measures can be objective or subjective and may not always correspond.[10] Absence of rebound after short-term use in healthy volunteers cannot exclude the possibility of long-term clinical difficulties in patients. Thus, large-scale outpatient studies may be needed to put the acute studies into perspective.

Withdrawal requires the study of a cohort of long-term users, preferably prospectively (although this raises major ethical problems). Assessment should be double blind (i.e., tapering and placebo substitution done at a time unknown to either patient or investigator). Cross-tolerance can be investigated with a "switch" study, (i.e., patients on long-term benzodiazepines are switched double blind to the agent under investigation).[11] Large-scale postmarketing surveillance studies may also be helpful, provided a rigorous procedure is followed so that the number of carefully sought withdrawal reactions can be related to clear estimates of the number of patients exposed to the medication. Although spontaneous reporting draws attention to a potential problem, it provides inaccurate estimates of the extent of a problem.

OLDER HYPNOTICS

Older hypnotics, such as chloral hydrate, barbiturates, and glutethimide, are primarily of historical interest. However, chloral hydrate is still favored by some practitioners, as is chlormethiazole.[12] Most of these compounds can cause withdrawal problems, and the barbiturates are also notorious for causing dose escalation. Occasionally, patients may be encountered who have developed dependence and experience withdrawal when stopping these drugs.[13]

Benzodiazepines

Studies on benzodiazepine rebound and withdrawal were primarily carried out between 1975 and 1990 and have been reviewed.[8,14] Most involve the double-blind administration of various benzodiazepines and a placebo to either healthy subjects or patients with insomnia for 1 to 28 nights, and then substitution of a placebo. Both polysomnographic and questionnaire data are used. However useful such studies are in detecting and quantifying rebound, they are of too short a duration to detect dependence. Very few studies have examined the withdrawal phenomena that might follow regular use of a benzodiazepine for more than 28 nights.

NONBENZODIAZEPINE HYPNOTICS

Zopiclone

Zopiclone, first introduced into clinical practice in 1987, has since been licensed in many countries with the notable exception of the United States. Long-term efficacy has been established. This agent has been used by tens of millions of patients and has been extensively studied. Large postmarketing surveys have evaluated its benefits and risks in day-to-day clinical practice.

In a small study of 11 people with chronic insomnia[15] who received zopiclone, 7.5 mg, for up to 8 weeks, 1 patient dropped out because of marked nighttime rebound and daytime anxiety. The latter can be a sign of dependence and withdrawal, although its importance, or even existence, has been disputed. Otherwise, no evidence of rebound was seen either on the sleep electroencephalogram (EEG) or subjective questionnaire replies in this study.

Long-term studies have been designed to detect withdrawal as well as rebound phenomena. A large-scale study in France[16] recorded any reactions to stopping zopiclone after 3 to 12 months. A total of 1284 patients took part; 1117 (87%) stopped abruptly. Of those who stopped abruptly, more than 100 patients reported adverse events, but only 17 (1.3%) presented substantial evidence of withdrawal. The most commonly reported symptoms, which definitely

constitute part of a withdrawal syndrome, were anxiety, irritability, malaise, and perceptual changes.

The study by Lemoine et al.[17] exemplifies the problem of withdrawal after long-term hypnotic use. These investigators ran 2 parallel studies; 1 with chronic zopiclone users and 1 with zolpidem users. Patients were randomly assigned either to continue or to taper medication, and various criteria were used to define withdrawal. Possible syndromes were found in 38% of patients who withdrew from zopiclone compared with 20% of patients who continued ($p = .008$). Most of the symptoms related to sleep complaints; if these were excluded, the difference between the groups was not significant. The authors also opined that these apparent withdrawal problems occurred much less frequently than with benzodiazepines. Zolpidem results are discussed below.

Benzodiazepines disrupt sleep patterns[18]; zopiclone has minimal effect on sleep patterns.[19] Patients switched from long-term benzodiazepine use to zopiclone showed normalization of the sleep EEG.[20] This finding led to a large study[11] in which 134 benzodiazepine users were switched to zopiclone with either a drug-free interval, an abrupt switch, or an overlapping drug regimen. Zopiclone improved both sleep and daytime alertness. All hypnotics were withdrawn 1 to 2 months after the medication change, and more than four fifths had remained off hypnotics at follow-up 12 to 18 months later. The authors concluded that zopiclone was a valuable tool in a withdrawal strategy and that abrupt switch was the optimal approach.

Postmarketing surveillance data have been obtained both formally and informally. A study from the United Kingdom logged prescriptions in 13,177 patients.[21] No withdrawal reactions were reported in those discontinuing their medication, nor did a smaller Spanish postmarketing surveillance study uncover any problems of withdrawal.[22] Pharmacovigilance surveys have detected some withdrawal problems, but these are usually secondary to abuse with resultant use of high doses (an uncommon situation).[23] In rare instances, convulsions can be part of a withdrawal syndrome, but the risk is low.

After a review of 25 zopiclone discontinuation studies, Bianchi and Musch[24] concluded that stopping this drug does not appear to result in rebound effects or significant symptoms of withdrawal. This statement might seem too broad, but the evidence to date suggests that both phenomena are uncommon and do not constitute any more than a minimal clinical problem. The data still indicate that any such difficulties encountered by the patient are notably less than those attending the withdrawal of equivalent benzodiazepines.[25]

Zolpidem

In addition to being efficacious for insomnia, zolpidem is claimed to induce and preserve the physiologic architecture of sleep and also to be devoid of tolerance, dependence, and rebound phenomena.[26] These assertions are backed by a portfolio of studies.[3] Zolpidem has an elimination half-life of around 2 to 3 hours and is also selective on the benzodiazepine subtype 1 receptor. However, it is unclear how this translates into any clinical benefit.

A few long-term studies have addressed the question of possible withdrawal and dependence. The Lemoine et al. study[17] discussed earlier also incorporated a group of patients who received 10 mg of zolpidem every night for at least 3 months. After discontinuation, withdrawal phenomena were sought using various criteria. As with the zopiclone users in the parallel study, most putative withdrawal features were related to insomnia rather than to any newly emergent symptoms. Schlich et al.[27] studied 107 patients with chronic insomnia aged 40 to 86 years. Patients received up to 20 mg of zolpidem for 180 nights, followed by 10 nights of placebo withdrawal. No rebound was detected, and even in the placebo period, measures of sleep efficacy remained improved over pretreatment baseline. In another 180-night study,[28] the improvement in some sleep measures was maintained, and neither rebound nor withdrawal supervened.

Against these formal studies are arrayed a few case reports of withdrawal and dependence with zolpidem.[29] In 2 of these reports, escalation of dosage had occurred,[30,31] but not in a third.[32] However, the sporadic nature of these published cases suggests that such events are uncommon.

As with zopiclone, several studies have evaluated the usefulness of zolpidem in facilitating withdrawal from long-term benzodiazepine hypnotic use.[33] Both gradual and abrupt transitions were used. Two preliminary studies suggested the possibility of transferring most patients on long-term hypnotics to zolpidem. Subsequent withdrawal also seemed to be easier.[34,35] A controlled double-blind trial of 84 patients confirmed the usefulness of this strategy in facilitating withdrawal from long-term triazolam use.[33]

Zaleplon

The withdrawal profiles of zolpidem and zaleplon are similar. Zaleplon has been shown to be effective over a period of 35 nights with no evidence of tolerance or discontinuation effects.[36] Rebound insomnia has not been detected in the studies during development,[36–41] nor did studies show a risk of dependence.[38–40] One long-term, open-label extension study[42] reported that zaleplon was well tolerated with no evidence of withdrawal effects after 52 weeks of nightly use. Similar tolerability was found in a 6-month open-label extension study of nightly use of zaleplon in the elderly.[43] With such rapid elimination, the target receptors are probably inactivated most of each 24 hours. If the potential to use zaleplon only when symptoms occur were routinely employed,[44] as an intermittent adjunct to behavioral interventions,[45] the risk

for dependence, and thus withdrawal symptoms, may be minimized.

PRACTICAL IMPLICATIONS

Advice to withdraw hypnotic medication should follow a careful evaluation of self-reported sleep patterns, psychological factors, and psychosocial status. Ideally, every long-term hypnotic user would have at least 2 nights in a sleep laboratory, but this is not feasible, so decisions must be made on clinical judgments. Ambulatory monitoring, however, is fast becoming a practical possibility when coupled with computerized analysis of the recordings. Before withdrawal, a careful psychiatric assessment should reveal the presence of clinically significant anxiety or depression. Both should be treated with an antidepressant before withdrawal is attempted. Although the optimal tapering schedule will depend on the individual patient, 8 to 12 weeks should be the usual goal. Special formulations of hypnotics may be needed, and liquid preparations provide the greatest flexibility. Prior explanation, repeated reassurance, mobilization of caregivers, and frequent monitoring are the cornerstones of success. As this review indicates, substitution of zopiclone or zolpidem may facilitate withdrawal from other hypnotics, but should be reserved for those who fail to complete a simple tapering regimen.

In the longer term (> 28 nights), a disturbing number of carefully controlled studies show a waning of efficacy (i.e., pharmacologic tolerance), particularly with respect to polysomnographic variables. However, efficacy was found to persist for 35 nights in 1 polysomnographic study.[36] Long-term use is common, especially in the elderly. The newest compounds are probably no exception to this waning of objective efficacy after several weeks of nightly administration. The maintenance of subjective efficacy is also only partial. Rebound and withdrawal after the use of benzodiazepine hypnotics must be seen as probable major factors in perpetuating hypnotic use. Long-term data with the newer compounds are still relatively sparse. Although expensive and difficult to obtain, evidence for long-term efficacy is much needed. The risk:benefit ratio of all hypnotics must be presumed to change adversely with long-term use according to the patient and the drug.

This raises the question of how to avoid moving inadvertently from short- to long-term use. Setting limits on short-term use is generally suggested, but in practice such limitations can make the patient fearful that the insomnia might worsen. Hypnotic medication should be used short term as respite medication to enable a full assessment of the insomnia and to try other methods of management, such as sleep hygiene and the psychological techniques discussed elsewhere in this publication. Regardless, all this requires education of patient and doctor, a reappraisal of the insomnia problem by society at large, and the allocation of adequate resources.

Abuse Potential

Abuse potential is difficult to predict from preclinical or healthy-subject data. Nevertheless, there are models that are helpful. One study[46] compared the acute behavioral effects and abuse potential of trazodone (100 mg, 200 mg, 300 mg), zolpidem (15 mg, 30 mg, 45 mg), and triazolam (0.25 mg, 0.5 mg, 0.7 mg) in 10 male volunteers with histories of alcohol and drug abuse. Both triazolam and zolpidem increased scores on various subjective ratings indicative of pleasant euphoric effects. However, this was marked only at the 45 mg dose of zolpidem, several times the recommended dose. Trazodone had fewer effects.

A second study from this group[47] compared zaleplon and triazolam in volunteers with histories of substance abuse. The zaleplon doses were 25 mg, 50 mg, and 75 mg, compared with the licensed dose of 10 mg. Again, euphoriant effects were detected. By contrast, triazolam was administered at doses of 0.25 mg, 0.5 mg, and 0.75 mg, much closer to the usual clinical dose range, rendering the comparison somewhat biased. Both zolpidem and zaleplon appear to induce euphoriant effects at supratherapeutic dose levels, whereas triazolam has effects at doses much closer to those used in practice.

How precisely such studies can predict actual abuse potential remains unclear. Many observations have confirmed the abuse liability of benzodiazepines.[48] Some addicts reportedly will abuse zopiclone, if it is available. However, most of the abuse reports involve addicts transferring from benzodiazepines, such as temazepam and flunitrazepam, because they have become less available due to stricter scheduling. Reports of abuse involving zolpidem are rare, a fact that may reflect its short duration of action. Logically then, zaleplon should be even less likely to be abused because, even at high doses, the psychotropic effects would be short lived.

CONCLUSION

Insomnia is a complex and ill-understood complaint that is associated with quite distressing symptoms of inefficient functioning as well as objective impairments. Chronic primary insomnia is common, and its treatment is controversial. Long-term treatment with hypnotic drugs is of unestablished efficacy, and tolerance probably occurs. With risks of rebound and withdrawal, the risk:benefit ratio for benzodiazepines becomes adverse after about 2 weeks of continuous administration. Based on current evidence, newer compounds, such as zopiclone, zolpidem, and zaleplon, appear less likely to be associated with rebound and withdrawal than short-acting benzodiazepines, making them important alternatives and the treatment of choice for many patients.

Drug names: temazepam (Restoril and others), trazodone (Desyrel and others), triazolam (Halcion), zaleplon (Sonata), zolpidem (Ambien).

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