Primary Psychiatry. 2010;17(7):28-30

The Latest Insomnia Medications: *What's Old is New*

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People have tried ingesting so many different substances in the desperate attempt to sleep. The use of alcoholic beverages and opium-based concoctions go back millennia. Chloral hydrate and barbiturates have been around for over 100 years. Several effective sedating medications appeared during the last century, but disappeared due to abuse and other serious safety problems. In recent decades, the primary Food and Drug Administration-approved medications recommended for the treatment of insomnia have been the benzodiazepine receptor agonist (BZRA) hypnotics, including the original benzodiazepines (eg, flurazepam, temazepam, and triazolam), and the subsequent nonbenzodiazepines (eg, eszopiclone, zaleplon, and zolpidem). The first new mechanism-of-action insomnia medication approved by the FDA for decades was the selective melatonin receptor agonist, ramelteon, which became available ~5 years ago. All of the FDA-approved insomnia medications had been immediate-release capsules or tablets that were shown to benefit sleep onset and, depending on the pharmacokinetics, possibly sleep maintenance. Until recently, the only exception was the 2005 approval of an extended-release tablet formulation of zolpidem. In addition to the medications specifically approved by the FDA for the treatment of insomnia, physicians have prescribed an assortment of sedating medications to promote sleep in insomnia patients. Mostly these have been antidepressants and antipsychotics. People also have taken prescription-strength or over-the-counter doses of antihistamines, mostly diphenhydramine, as sleep aids or for the treatment of insomnia.[1]

Why have I suggested that what is old is new? The answer is because all of the most recent FDA insomnia medication approvals have involved entirely new formulations of older pharmaceutical agents. These new products include two oral alternate delivery formulations of zolpidem and a new very low dose version of the tricyclic antidepressant, doxepin.[2-4]

ZOLPIDEM ALTERNATE DELIVERY: *EDLUAR AND ZOLPIMIST*

Zolpidem, a relatively short half-life nonbenzodiazepine BZRA hypnotic, first became available in the United States in 1993 as the brand name product Ambien and then in generic versions beginning in 2007. The official immediate-release zolpidem indication is for the short-term treatment of insomnia characterized by difficulties with sleep initiation. In contrast, the zolpidem extended-release (Ambien CR) indication is for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Note the absence of a limitation on the duration of use with the extended-release formulation.

In December 2008, the FDA approved dissolvable tablet and oral spray formulations of zolpidem. These two alternate delivery immediate-release versions were developed using the shortcut FDA drug development 505(b)(2) pathway, which is intended for changes in the dosage form, strength, or route of administration of previously approved medications. By employing this drug development route, pharmaceutical companies

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Disclosure: Dr. Neubauer has served as a consultant to sanofi-aventis.

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do not need to spend the millions of dollars and several years typically required for extensive animal and human efficacy and safety studies. However, the FDA generally does require pharmacokinetic studies demonstrating the bioequivalence of the new formulation and the original drug doses. Since FDA approval is based on the previously approved medication, the new formulation generally has the same indication as the old drug—in this case, 5 mg and 10 mg doses for the short-term treatment of sleep-onset insomnia. These new alternate delivery zolpidem versions also share the same immediate-release zolpidem prescribing information regarding contraindications, warnings and precautions, adverse reactions, drug interactions, and use in specific populations. Similarly, the new formulations both are intended for bedtime use and are classed as Schedule IV controlled substances by the Drug Enforcement Agency.

Edluar, the dissolvable tablet zolpidem formulation is available in pharmacies and is manufactured in 5 mg and 10 mg tablets.[2] ZolpiMist, the oral spray formulation, was developed by NovaDel Pharma and should be available in the near future. ZolpiMist will come with a metered-dose pump assembly providing 5 mg of zolpidem with each actualization. Therefore, two sprays at bedtime represent the standard adult dose. Specific instructions on how to prime the pump will accompany the child-resistant, 60-spray containers.[3]

Are there potential advantages to these two new unique hypnotic formulations? People who have difficulty swallowing pills may appreciate them. There being no need for water to take the doses could be helpful in some situations. It might be argued that they allow a more rapid onset of action through direct oral absorption and by avoiding the delays of the gastrointestinal-hepatic route. However, with both new formulations, absorption is significantly delayed following a meal compared with the fasting condition. This evidence argues that gastrintestinal absorption is a major component. If the empty-stomach absorption is somewhat faster with these new products, it may be that they are swallowed as liquids and there is no delay associated with a pill dissolving in the stomach. Ultimately, clinical experience will provide the onset-of-action answer. Consideration also will have to be given to potential disadvantages of a hypnotic's very rapid onset of action.

LOW-DOSE DOXEPIN: *SILENOR*

In March 2010, the FDA granted approval of 3 mg and 6 mg dose tablets of doxepin for the treatment of insomnia characterized by difficulties with sleep maintenance. These low doses of doxepin were developed for the treatment of insomnia by Somaxon Pharmaceuticals and they will be marketed with the brand name Silenor. The specific approval of doxepin for treating insomnia is unusual since the medication at higher doses has been available for the treatment of depression since 1969. For decades, doxepin has been manufactured in doses ranging from 10–150 mg and the prescribing guidelines for depression go as high as 300 mg/day. Since this new approval of doxepin involved a new therapeutic indication and previously unapproved doses, extensive safety and efficacy testing was required. Clinical trials have been performed with both adults and older adults. The FDA-approved indication does not include any limitation on the duration of use. Since doxepin has no abuse liability, it is not classed by the DEA as a controlled substance.[4]

Why low-dose doxepin for the treatment of insomnia? Histamine is a key central nervous system (CNS) wake-promoting neurotransmitter originating in neurons of the tuberomammillary bodies of the posterior hypothalamus. Neuronal networks within the hypothalamus play critical roles in the regulation of sleep and waking.[5] Centrally acting antihistamines tend to be sedating. Doxepin is highly selective for histamine-1 receptor antagonist activity and at low doses the potential side effects associated with other receptor activities are minimized. Doxepin's role as an antihistamine is evident in the fact that for many years the drug's formulations have included a topical cream intended to treat pruritus.

The clinical trials for these low doxepin doses demonstrated that it was especially beneficial for sleep maintenance, including the final third of the night. Although the elimination half-life of doxepin is ~15 hours, next-morning sedation was not a major problem. That may be due to the low dose, but possibly also because of circadian-timed, wake-promoting effects of other neurotransmitter systems at a person's typical morning wake up time.

The Silenor prescribing information suggests initial 6 mg doses for adults and 3 mg for elderly patients to be taken within 30 minutes of bedtime, but not within 3 hours of a meal.[4] Pharmacokinetic studies demonstrated that the postdose peak serum concentration in fasting healthy subjects taking the 6 mg dose occurs after ~3.5 hours. It was delayed a further 3 hours when the dose was taken following a high-fat meal.[4]

Somnolence/sedation, nausea, and upper respiratory tract infection were the treatment-emergent adverse reactions in the clinical trials occurring in ≥2% of the low-dose doxepin subjects compared with the placebo groups. The contraindications are hypersensitivity to the ingredients, co-administration with a monoamine oxidase inhibitor, and untreated narrow angle glaucoma or severe urinary retention. There is no black-box warning for suicidality, as

exists with the higher doxepin doses. However, the warnings and precautions do note the potential for worsened depression and an increased suicide risk; CNS-depressant effects; and abnormal thinking, behavioral changes, and complex behaviors (eg, "sleep driving" and hallucinations). It is Pregnancy Category C. Abrupt discontinuation of the medication is not associated with a withdrawal syndrome.[4]

COMMENTARY

These three recently approved insomnia medications all have new features, although each is based upon previously available compounds with well-established pharmacodynamic properties. While the zolpidem indications are for sleep-onset difficulty and the low-dose doxepin for sleep maintenance, the benefits for individual patients may not be entirely predictable. Some patients taking the zolpidem formulations likely will experience improved sleep maintenance, just as some using the low-dose doxepin will fall asleep more rapidly. New additions to our insomnia pharmacopoeia certainly are welcome. The low-dose doxepin provides another nonscheduled option. The new zolpidems may offer some dosing flexibility.

Might either new zolpidem formulation be useful for middle-of-the-night (MOTN) awakenings with difficulty returning to sleep? Neither these nor any other insomnia medications presently have a specific FDA indication for MOTN dosing. If any pharmaceutical companies hope for an appropriate FDA indication to promote MOTN use, they will need to perform extensive efficacy testing and demonstrate the safety of the dosing with less than a full night available for sleep. The FDA will want clear evidence that MOTN dosing does not cause next-morning impairment. Transcept is developing a low-dose sublingual zolpidem formulation specifically intended for as-needed MOTN use.[6] In a March 2010 press release, the company announced plans for a 1-hour highway driving study to assess potential next-day residual effects. NovaDel Pharma also has announced plans to investigate low-dose ZolpiMist for a possible future MOTN indication.

No other new insomnia medication approvals are anticipated in the immediate future; however, a variety of novel compounds are being evaluated in efficacy and safety studies for the treatment of insomnia. The most developed among these are orexin receptor antagonists. Stay tuned for further updates as more evidence becomes available. ***PP***

REFERENCES

1. Neubauer DN. The evolution and development of insomnia pharmacotherapies. *J Clin Sleep Med*. 2007;3(5 suppl):S11-S15.
2. Edluar [package insert]. Somerset, NJ: Meda Pharmaceuticals; 2009.
3. ZolpiMist [package insert]. Bridgewater, NJ: NovaDel Pharma Inc; 2008.
4. Silenor [package insert]. Solana Beach, CA: Somaxon Pharmaceuticals Inc;. 2010.
5. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437(7063):1257-1263.
6. Roth T, Hull SG, Lankford DA, Rosenberg R, Scharf MB, Intermezzo Study Group. Low-dose sublingual zolpidem tartrate is associated with dose-related improvement in sleep onset and duration in insomnia characterized by middle-of-the-night (MOTN) awakenings. *Sleep*. 2008;31(9):1277-1284.