A new class of sedative/hypnotics: Dual orexin receptor antagonists

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The management of insomnia in the elderly presents ongoing challenges. Ideally, nonpharmacologic approaches such as improving sleep hygiene will help improve sleep without annoying and potentially dangerous side effects, however, seniors often resort to pharmacologic treatment or remain untreated. I shudder to think back at how we treated insomnia when I first started practicing as a nursing home consultant pharmacist. The powerful sedative/hypnotics pentobarbital (Nembutal®) and secobarbital (Seconal®) were routinely used along with chloral hydrate (Noctec®) and a few others. These products would indeed induce sleep but also frequently cause significant side effects including excessive sedation and residual drowsiness resulting in falls and fractures.

Over the years, the pharmacology and treatment of sleep have improved with the advent of newer medicines that act more specifically on sleep centers rather than globally suppressing the central nervous system. Benzodiazepines were commonly used for a period of time but, because of unacceptable side effects, they fell out of favor and were replaced by newer and potentially safer products including zolpidem (Ambien®), zaleplon (Sonata®), and eszopiclone (Lunesta®). These products were embraced by geriatric clinicians; however, since they potentiate the activity of gamma amino butyric acid and have numerous effects in the brain, they may cause unwanted side effects such as psychomotor and memory impairment. In fact, as I reported in my July, 2014 column in Geriatric Nursing, dosage reductions were recently recommended for these products because of increased recognition of side effects.

As scientists have continued to study the chemistry of sleep they have learned that the orexin system is a key regulator of sleep and wakefulness. They discovered that a deficiency of the neuropeptides, orexin-A and orexin-B, results in narcolepsy and found that if these chemicals are blocked by orexin antagonists, improved sleep will result. Since these orexin inhibitors target a more localized area in the brain it is hoped that they will cause fewer side effects than the existing agents.

Research has continued and we will soon see a new class of sleep aids coming to market, in fact, in August, 2014, the first dual orexin receptor antagonist (DORA) was approved for human use by the US Food and Drug Administration. Suvorexant (Belsomra®) is a new prescription drug indicated for the treatment of insomnia characterized by difficulty with sleep onset and/or sleep maintenance. Belsomra® will be available in 2015.

Belsomra® comes in four strengths – 5, 10, 15, and 20 mg tablets. I find the prescribing information a little confusing because it is recommended to “use the lowest dose effective for the patient” but at the same time it states that the recommended dose for “Belsomra® is 10 mg, taken no more than once per night and within 30 min of going to bed, with at least 7 h remaining before the planned time of awakening.” It further states that “The maximum recommended dose of Belsomra® is 20 mg once daily.” The prescribing information does not address a specific geriatric dose, however, since most geriatric clinicians follow the well-known mantra, “start low and go slow” I suspect that we will frequently see therapy initiated with the 5 mg dose, although the prescribing information does state that clinically meaningful differences in safety or effectiveness were not observed between elderly patients and younger adults at the recommended doses. So, if a clinician starts low, by prescribing the 5 mg dosage and it is not effective, consideration should be given to gradually increasing the dosage. This appears to be a reasonable approach because, based on the prescribing information, including the clinical trials cited, it appears that at least some elderly patients will be able to tolerate higher dosages.
The most commonly reported adverse reaction reported by clinical trial participants taking Belsomra® was drowsiness. Medications that treat insomnia can cause next-day drowsiness and impair driving and other activities that require alertness. People can be impaired even when they feel fully awake.

Animal studies have determined that DORAs have a wider therapeutic margin for sleep versus cognitive impairment compared to zolpidem, eszopiclone, and diazepam.3 Belsomra® tablets are film coated and unscored. I contacted the manufacturer to see if they had any information on whether the tablets could be crushed and/or mixed in a food such as apple sauce. I routinely ask this question when a new drug comes to market and, to no surprise, their response was that they had no data on this practice but it is not recommended. While crushing and mixing have not been studied, and these practices are not recommended by the manufacturer, I assume that some nurses will crush and/or mix if they experience difficulty administering the product. This is a common practice in senior care and I continue to recommend that drug companies research this practice and have the information available when a new product is marketed.

In the completed clinical trials there was no reported evidence for physical dependence with prolonged use of Belsomra® and no reported withdrawal symptoms after discontinuation. Likewise, no clear effects were observed on measures of sleep onset or maintenance following discontinuation which indicates that this product is not associated with rebound effects.

Four clinical trials evaluated the effect of nighttime administration of Belsomra® on next-day memory and balance. Three of these trials showed no significant effect but the fourth showed a significant decrease in word recall in healthy non-elderly subjects following a single dose of 40 mg of Belsomra®. However, it must be pointed out that 40 mg is twice the maximum approved dosage. This study also showed a significant increase in body sway following a single dose of 20 or 40 mg of Belsomra®.

Interestingly, the effect of Belsomra® on “middle of the night safety”, a keen area of interest in geriatrics, was assessed by a double-blind, randomized, placebo-controlled trial that evaluated the effect of a single 30 mg dose of Belsomra® on balance, memory and psychomotor performance in 12 healthy elderly subjects after being awakened during the night. The study found that there was impairment of balance at 90 min compared to placebo but no impairment of memory. Again, it must be pointed out that the 30 mg dose used in this study was larger than the maximum FDA approved daily dose of 20 mg and it is likely that many geriatric patients will be taking doses less than 20 mg which would be likely to have less effect on balance.

While it is too early to come to firm conclusions about this product specifically or the DORA class in general, I must admit that these limited data have my attention. In theory, the high degree of specificity and unique mechanism of action could result in a class of drugs that offer at least incremental improvements in safety and efficacy compared to existing agents. Obviously we really won’t know if this is true until the product is available and significant clinical experience has been gained, especially in the frail elderly adult population who will be likely users of Belsomra® and other drugs in this class which will likely come to market in the future.

References