Patient Safety Tip of the Week

June 3, 2014

More on the Risk of Sedative/Hypnotics

In our What's New in the Patient Safety World columns for May 2012 "Safety of Hypnotic Drugs" and November 2012 "More on Safety of Sleep Meds" we discussed the issue of a possible link between sedative/hypnotic drugs and mortality. One study (Kripke 2012) found the risk for death was about 4.5 times higher in those patients who had been prescribed hypnotics. They found a dose-response relationship where the risk increased with increasing numbers of sleep pills taken. A second paper by the same group and same database found that the risk of death was even higher in the subset of patients having obesity (Langer 2012). The authors speculated about the role of sleep apnea and its interaction with the sleep meds in this population. While those two studies may have uncovered an association between mortality and use of hypnotics, they do not confirm a cause-effect relationship.

Another study challenged the strength of the association between hypnotic use and mortality (Hartz 2012). One key question unanswered in previous studies showing a higher mortality in patients using hypotics was whether sicker or higher risk patients were more likely to use these drugs. The Hartz study used data from the well-known long-term Women's Health Initiative (WHI) and was able to adjust for a host of other clinical factors. They did note that those women using almost daily hypnotic drugs had a 62% increased risk of mortality. However, after adjusting for a variety of risk factors associated with poor health there was a great attenuation of the relationship between hypnotic use and mortality (adjusted odds ratio 1.14) for those using hypnotics almost daily and the relationship disappeared entirely for those using them less frequently. However, since the study period for the WHI ended in 1998 most women in the study did not take any of the currently used sedative/hypnotic agents that may have been used in the more recent studies.

Now a new study again notes an association between anxiolytic and hypnotic medications and increased mortality (Weich 2014). Researchers in the UK, using the General Practice Research Database were able to compare mortality risks in over 100,000 patients prescribed anxiolytics or hypnotic medications compared to age- and sex-matched controls followed for a mean of 7.6 years. They found that mortality rates for those patients prescribed such drugs were over three times higher than those not taking such medications, even after adjustment for likely confounding factors. Moreover, there

appeared to be a dose-dependent association in that the mortality rates were even higher in those taking such drugs for at least 90 days per year. While benzodiazepines were the most widely prescribed and had the highest association with mortality, the association and dose-dependent effect were seen for all drugs studied, including the so-called "Z drugs" (zolpidem, zaleplon, and zopiclone). The authors do point out that, because this is an observational study, confounding due to unknown factors cannot be excluded. Also, they cannot exclude a bias related to indications for prescribing such drugs.

Over the years we've discussed many of the safety issues related to sedative/hypnotic drugs (see the links to prior columns below). They frequently are contributing factors to patient falls, hip fractures, delirium, and opioid-related respiratory depression. Sometimes we'll see withdrawal syndromes in patients who have been receiving such drugs chronically. They may also play a role in predisposing some patients to aspiration. Anecdotally, they are a frequent contributor to events occurring in patients with sleep apnea and a recent study (Li 2014) demonstrates a reliable association between a history of high-dosage hypnotics and sleep related breathing disorders. Zolpidem has been associated with increased visits to the emergency department and another recent study (Huang 2014) has shown an association between zolpidem use and infections.

And, of course, sedative/hypnotics have been linked to next-day impairment of activities requiring mental alertness, such as driving. In our March 2013 What's New in the Patient Safety World column "Sedative/Hypnotics and Falls" we noted that the FDA (FDA 2013) had recommended lower doses of certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist) because of potential next-day impairment of activities requiring mental alertness, such as driving. Just recently the FDA (FDA 2014) issued a similar alert recommending lower doses for eszopiclone (Lunesta). The FDA cited studies in healthy adults showing next-morning psychomotor and memory impairment after dosing with 3 mg. eszopiclone compared to placebo and that such impairments were most severe at 7.5 hours but still present 11 hours after dosing. The new FDA recommendation is for a starting dose of Lunesta of 1mg. at bedtime.

While the nature of most studies linking sedative/hypnotic drugs to these undesirable outcomes precludes conclusion of a cause-and-effect relationship, the frequency with which these associations appears in observational and retrospective cohort studies is strong enough to make you question prescribing these drugs for your patients. Prescribing sleep meds, whether for inpatients or outpatients, is often done without much thought. All too often they are thought of as being relatively harmless. Knowing the potential downside is an important first step. On the inpatient side, putting in place various system fixes (eg. removing them from standardized order sets, using clinical decision support tools, etc.) may play a more important role. On the outpatient side, knowing and understanding how to promote good sleep hygiene is extremely important in helping patients avoid the need for such drugs in the first place. You need to help patients adopt practices that promote good nocturnal sleep. That includes things like counseling them about eating and drinking habits in relation to time of day (eg. avoiding caffeinated beverages at night or avoiding large volumes of fluid that will lead to awakening to void).

And you need to make sure that noise and light levels are not barriers to sleep and that the ambient temperature is conducive to sleep. Similarly, activities earlier in the day may be important. Getting some exercise, particularly outdoors, may benefit sleep as well as overall health. Attention to patterns of any naps may also identify why a patient has trouble sleeping at night.

Some of our previous columns on safety issues associated with sleep meds:

August 2009	"Bold Experiment: Hospitals Saying No to Sleep Meds"
March 23, 2010	"ISMP Guidelines for Standard Order Sets"
May 2012	"Safety of Hypnotic Drugs"
November 2012	"More on Safety of Sleep Meds"
March 2013	"Sedative/Hypnotics and Falls"
June 2013	"Zolpidem and Emergency Room Visits"
August 6, 2013	"Let Me Sleep!"

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