Pain Medicine

Pain Medicine 2010; 11: 801–802
Wiley Periodicals, Inc.

EDITORIAL

Considering the Risks of Benzodiazepines and Opioids Together

Co-administration of benzodiazepines and opioids is frequent, yet little is known about the interactions or potential outcomes of the combination. It is with kudos, then, that the scientific pain community receives a large prospective study of independent variables and opioid use, with a particular focus on benzodiazepines, the results of which are published in this issue.

Using a cohort of more than 17,000 men and women followed for 4 to 7 years, Norwegian investigators Skurtveit and colleagues looked at recent opioid prescriptions for subjects who had earlier reported using benzodiazepines but no opioids. They came to the intriguing conclusion that benzodiazepine use contributes to later opioid use among subjects who had reported no opioid use to start. In fact, benzodiazepine users were more than seven times as likely to have at least 12 prescriptions for opioids than non-benzodiazepine users during the follow-up period. Controlling for pain and other potentially confounding factors reduced the benzodiazepine effect, yet users were still three times more likely to later user opioids than were nonusers.

As always, good research poses still more questions. A difficulty in interpretation arises because the use of opioids is not clearly characterized. Were opioids consumed in the context of compliant pain management, overused in relation to pain complaints, taken recreationally, or used in some combination? The limits of the study's structure does not provide for such detail. Neither is it known how frequently subjects were using benzodiazepines and in what amounts. Still, the finding of an association between benzodiazepine and opioid consumption is significant, and attention to the combination is overdue given that particular risks apply to patients being treated for chronic noncancer pain.

It could be, for example, that benzodiazepines as a family of medications with addictive properties confer vulnerabilities to misuse substances in genetically and environmentally vulnerable people. Evidence supports that misusers of one substance are likely to misuse another substance or substances as well [1].

It could also be that patients who are prescribed benzodiazepines exhibit characteristics that present their own risks for chronic pain, opioid misuse, medication overuse, or any combination of those factors. Mental-health disorders, including anxiety for which benzodiazepines are prescribed, are associated with heightened pain and opioid use [2]. Evidence is increasing that mental-health disorders present risks for opioid-related problems even in patients who have a significant co-occurring pain problem [3]. Mood disorders increase vulnerability to addiction and vice versa in a circular relationship the National Institute on Drug Abuse terms "overlapping conditions—shared vulnerability [4]."

Furthermore, a recent Utah report of patient characteristics in unintentional opioid-related deaths showed that in 240 deaths that involved no illicit drugs, 49% of decedents were reported to have suffered from a mental illness, 14% of those from an anxiety disorder [5]. A majority of these decedents had used medications to help them sleep, another frequent indication for benzodiazepines.

Together, these observations are not meant to imply that all patients with chronic noncancer pain have mental-health disorders or that opioids confer mental disorders. They do indicate, however, that subgroups of vulnerable patients exist whose genetic predispositions once triggered may be exacerbated by environmental conditions. Such patients deserve special considerations whenever opioid therapy is weighted.

The fact that benzodiazepines make frequent appearances as co-intoxicants in opioid-related deaths presents yet another risk. Skurtveit et al. mention their previous report showing a dose-response relationship between the frequency of benzodiazepine use and total mortality [6]. Although the effect is moderated when lifestyle and socioeconomic factors are controlled for additional evidence buffers the finding. In 2006, about half of all U.S. opioid-related deaths involved more than one type of drug with benzodiazepines mentioned most frequently, being involved in 17% of the deaths [7]. The frequent mention of benzodiazepines in opioid-related mortality data is confirmed in the Utah report [5].

Many people use benzodiazepines as needed without risk of harm and with substantial benefit. However, Skurtveit et al. conclude that benzodiazepines and opioids together make for a risky combination and write, "This combined use is regarded as particularly problematic for addiction potential." As we consider evidence from other sources that bolsters this claim, it is also worth noting that the

authors concede that benzodiazepine users reported more disability, cardiovascular disease and musculoskeletal pain than non-users, suggesting chronic illness at baseline that could logically precipitate opioid use.

As always, balancing risk with benefit is fundamental. In that interest, initial and ongoing mental-health assessments in association with opioid therapy are critical. When treating pain with opioids, most compassionate, competent clinicians are aware that treatment of comorbidities such as anxiety disorders and insomnia contribute to better outcomes. However, given the risks of co-medication using opioids and benzodiazepines, clinicians might want to consider when possible using an alternative to benzodiazepines or else consider limiting the amount of opioids used for pain.

LYNN R. WEBSTER, MD
Lifetree Clinical Research & Pain Clinic Salt Lake City, Utah

References

1 Tsuang MT, Lyons MJ, Meyer JM, et al. Co-occurrence of abuse of different drugs in men: The role of drug-specific and shared vulnerabilities. Arch Gen Psychiatry 1998;55(11):967–72.

2 Sullivan MD, Edlund MJ, Zhang L,Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med 2006;166(19):2087–93.

3 Wasan AD, Butler SF, Budman SH, et al. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. Clin J Pain 2007;23(4):307–15.

4 Research Report Series from the National Institute on Drug Abuse (NIDA). *Comorbidity: Addiction and other mental illnesses*. December 2008. National Institutes of Health (NIH), U.S. Department of Health and Human Services. NIH Publication Number 08-5771.

5 Johnson E. Utah drug overdose mortality: Findings from interviews with family and friends of Utah residents aged 13 and older who died of a drug overdose between October 26, 2008 and October 25, 2009. *Utah Department of Health*. Available at: http://health.utah.gov/prescription/advisory%20committee/UtahDrugOverdoseDecedentInterviewsReport2009.pdf (accessed April 2010).

6 Hausken AM, Skurtveit S, Tverdal A. Use of anxiolytic or hypnotic drugs and total mortality in a general middle-aged population. Pharmacoepidemiol Drug Saf 2007;16(8):913–18.

7 Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999–2006. NCHS Data Brief 2009;22:1–8.