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COMMENTARY

Patterns of Zolpidem Use in Male and Female Veterans Following Revised FDA Dosing Guidelines

Commentary on Kim et al. Responsiveness of Veterans Affairs Health Care System to zolpidem safety warnings. *J Clin Sleep Med.* 2018;14(7):1135–1141.

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Insomnia is one of the most frequently reported symptoms in Veterans and can result in significant distress and adversely impact performance and functioning.[1–5] Zolpidem has been used for decades to treat insomnia and was formally placed on the VA formulary in August 2007, making it widely available within the VA Healthcare Administration (VHA). Hypnotics such as zolpidem act by increasing the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) activity and cause generalized central nervous system (CNS) suppression.[6] As a benzodiazepine receptor agonist, zolpidem has been preferred to previous sleep aids such as older benzodiazepines because of its shorter half-life and lower dependency risk. However, the potential that zolpidem could interfere with next day cognition and performance raised questions about its suitability for use in Veterans returning to the social and occupational demands of civilian life.

A drug safety bulletin from the Department of Veterans Affairs Pharmacy Benefits Management (VA PBM) Services was issued in May 2007 recommending that zolpidem be used at doses no greater than 10 mg per day.[7–11] A drug safety warning released in January 2013 by the Food and Drug Administration (FDA) further cautioned against next day impairment and recommended that doses be decreased, particularly in women. This recommendation was followed by FDA labeling changes that differed by sex (eg, 5 mg for women and 10 mg for men immediate-release zolpidem products and 6.25 mg for women and 12.5 mg for men for extended-release zolpidem products).[12]

The labeling changes resulted from the important discovery of a link between blood levels of the drug and driving impairments.[13] Sex differences in the metabolism of zolpidem led to slower drug clearance and greater next day impairment in women compared to men.[13] The warnings were followed by a subsequent FDA report and action plan to enhance the collection and availability of demographic subgroup data.[14] Sex differences in pharmacokinetics and side effects highlight the need to include sufficient numbers of women in pharmacotherapy trials to ensure that data on efficacy, safety and tolerability of drugs are evaluated in both men and women and that sex-appropriate dosage recommendations can be made.

Until recently, the potential for sex differences has not been a critical concern in the VHA that has traditionally provided care primarily for male Veterans. However, the need to adapt to the changing composition of VA health care users is critical. Women are exposed to more conflicts around the world than ever before. As of 2015, there were approximately 2 million women Veterans representing 9.4 percent of the total Veteran population, a number expected to increase by approximately 18,000 women per year for the next 10 years.[15] The VHA is in the process of adapting to meet the needs of the growing numbers of women Veterans.

The translation of dosage recommendations that differ for men and women to clinical practice is critically important. In this issue of the *Journal of Clinical Sleep Medicine*, Kim and colleagues present findings on prescriptions in the VHA following the zolpidem safety warnings.[16] Using an interrupted time-series design the authors examined monthly outpatient use of (1) *higher-than-recommended dose* of zolpidem among zolpidem users and (2) *any dose* zolpidem among all VHA users. Sensitivity analyses compared prescribing of zolpidem to other sleep medications not subject to safety warnings. The authors found that although there was a decrease in high-dose zolpidem use with each warning, after the 2013 FDA warning, roughly half of female Veterans remained on high doses. The major concern highlighted by this research is that despite the FDA warning, women Veterans continued to receive prescriptions of high dose zolpidem.

This study is notable for several significant strengths, including the utilization of nationally representative data using national-wide VA pharmacy records and data obtained from the VHA Corporate warehouse. Kim and colleagues examined data from almost 9 years obtained across 142 medical centers. Another strength was the quasi-experimental design using interrupted time-series analysis and consideration of facility region and rurality as well as potential compensatory prescribing changes with substituting sleep medications. This study is notable in that it highlights an important discrepancy between drug label changes and the translation of this information to clinical practice, particularly for women Veterans.

An unanswered question that remains is why did this discrepancy occur? There are inherent limitations in the interpretation of administrative data. For example, while this data tells us about prescriptions obtained through VA pharmacies, it does not ensure that patients took the medications as prescribed. Were some women patients cutting pills in half rather than changing the dose prescribed? Did clinicians recommend a trial of cutting the dose in half without changing the pharmacy order? We also do not know whether there were differences in prescribing based on specialty clinics. Was there better adherence to the label changes within VAs with dedicated women's clinics? The authors also point out that the overall declines in high and any dose zolpidem may have been related to the increase in availability of behavioral treatments for insomnia after the VA roll out of cognitive behavioral treatment for insomnia (CBT-I) in 2011. Were women less likely to seek out behavioral treatment for insomnia and if so, why?

The study by Kim and colleagues highlights the need to pay attention to sex-specific research findings and changes in treatment guidelines, and improve strategies to educate newer treatment guidelines to providers. Their work is particularly salient with respect to the increase in sex-specific research trials being conducted and with the likelihood of additional sex-specific dosage recommendations that may be warranted in the future. This will be a critical area of growth for VA providers who may be less accustomed to caring for female patients in a setting that has seen a dominantly male patient population. Given that women represent the fastest growing segment of Veterans seeking care it will be important to understand how to address the needs of women Veterans and provide more tailored sex-specific care. The report by Kim et al. is a critically important contribution to our understanding of VHA responsiveness to zolpidem safety warnings and to the care of women Veterans.

CITATION

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