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The Need for Pharmacovigilance in Sleep Medicine

Commentary on Vozoris et al. Sedative medication use: prevalence, risk factors, and associations with body mass index using population-level data. SLEEP 2011;34:869-874.

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Pharmacovigilance was defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problem.[1] Pharmacovigilance superseded the rather benign sounding phrase "drug monitoring" and places more emphasis on early detection and prevention of drug-related adverse consequences. While pharmacovigilance can be traditionally thought of as detecting adverse events related to side effects of medications, pharmacovigilance can also be applied to treatment failure, which can be gleaned from data mining information that ties prescription benefits with health care utilization.[2] One such example applies to therapeutic failure of macrolide antibiotics in respiratory infections that led to increased healthcare utilization, and was derived from analyses conducted on an integrated health-informatics database involving over 300,000 lives.[2] Alternatively, astute observations derived from published data led Topol and colleagues to uncover the association between rofecoxib (Vioxx) and myocardial infarction that was supported by biological plausibility.[3] Prescription trends with such medications spiked in certain susceptible populations that were engendered by marketing campaigns and direct consumer advertising.[4] Therefore the triangulation between prescription trends, targeted yet susceptible populations, and biological plausibility for potential harm can be considered as cornerstones of pharmacovigilance.

In line with such purpose, in this issue of *SLEEP*, Vozoris and Leung raise our awareness to the rising trend in prescription practices for sedative medications.[5] Moreover, they alert us to the fact that certain populations that are susceptible to the adverse effects of sedatives—such as morbidly obese men—are experiencing greater odds of sedative use and allude to the biological plausibility of potential harm.[6] There are other strengths to the work by Vozoris and Leung[5] that deserve close attention. The large sample size (nearly 400,000 participants) and high response rates to the questionnaire, the longitudinal study design (spanning prescription trends over a decade), adjustment for various known covariates, and the innovation in tapping an available health database to answer questions pertaining to sleep medicine are all worthy of praise. Moreover, their data stratified for gender suggesting obese men and underweight women as the drivers for the "U" shaped curved relationship between body mass index and prescription rates merits much attention. Specifically, such relationship parallels the previously reported U-shaped association between mortality and body mass index.[6] While some may attribute such a relationship to being mere markers for underlying disease, the probability for a causal connection should not be ignored.[7,8] The greater mortality rates driven by obese men with greater likelihood of sleep disordered breathing receiving sedatives cannot be ignored, but this area needs much more research. For example, there are some studies suggesting a dose-response relationship between severity of sleep disordered breathing and risk for motor vehicle accidents in patients with as yet undiagnosed sleep apnea who are receiving sedative medications.[9,10] Interestingly, in one of these studies there was a trend for patients with sleep apnea to be more likely to receive sedative medications than controls.[10]

How do we then determine if there are adverse consequences to sedative prescription practices? Unfortunately, randomized controlled trials to determine the adverse effects are not going to be performed for obvious ethical reasons. Also, the adverse effect profiles derived from clinical trials of sedative medications are less likely to yield valuable information, considering that they are limited in time and are tailored towards specific populations that are less susceptible to such adverse consequences. Moreover, such patients are closely monitored and counseled on the side effect profile when they participate in clinical trials. Consequently, the adverse events reported during clinical trials are less likely to detect the potential for harm as opposed to when the medications are prescribed "off-label" once they are available in the open market. The answer lies in building on the work of Vozoris and Leung.[5] Specifically, performing "real-world" comparative-effectiveness research by comparing mortality or other patient outcomes in disease registries that reside in the electronic data warehouses of integrated healthcare systems should be considered. While the study by Vozoris and Leung correlated the findings across the decade of data collection, they were unable to link such information to individual patient records or vital status records that would provide the healthcare utilization and mortality variables, respectively. The data infrastructure and charter for comparative effectiveness research was responsive to this very need and aimed to not only assess the relative benefits, but also to ascertain the relative *harms* of therapies.[11] Conceivably, comparing mortality outcomes in patients with insomnia re-

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ceiving cognitive behavioral therapy versus sedative medications while adjusting for "confounding by indication" using propensity scores[12] may shed light on this issue and direly needs to be done.

What should be done in the interim? Certainly nonpharmacological alternatives such as cognitive behavioral therapy (CBT) for managing chronic primary insomnia should continue to be considered as a first-line therapy for some patients.[13,14] Also, besides educating providers on identifying and treating sleep disordered breathing, the World Health Organization report on pharmacovigilance succinctly proposes that, "The risk of harm, however, is less when medicines are used by an informed health profession and by patients who themselves understand and share responsibility for their drugs."[1] This is particularly true in sleep medicine, wherein many of the sedating or wakefulness promoting agents can be double-edged swords, and the patients need to be educated on the shared responsibility of such therapies. Let us maintain the vigil over sleeping pills and ensure that our patients seek appropriate therapy.

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