COMMENTARY

Are Safety Warnings for Commonly-Used Sleeping Pills Reaching Those who Need them Most?

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When new evidence emerges of harmful effects of medicines, national regulators such as the U.S. Food and Drug Administration (FDA) often issue safety advisories to prescribers and the public, to inform them of the risks and of any needed changes to prescribing and use. A safety advisory is an important tool that aims to protect public health by ensuring that medicines are used as safely as possible. They are often accompanied by changes to the product's labeling, including boxed warnings if there is a risk of serious life-threatening harm.

Kesselheim and colleagues' study of users of two sleeping pills — zolpidem and eszopiclone — adds an important note of caution about how well these warnings protect public health.[1] The FDA issued two drug safety communications on zolpidem in 2013 on next-day impairment, cautioning against the use of high doses, and specifically highlighting the need for lower doses in women.[2] In 2014, the FDA also warned of next-day impairment with high doses of eszopiclone.[3]

For such warnings to be effective, users and prescribers need to be aware of the information, convinced of the need to shift towards safer use, and able to make these changes. In this national U.S. survey of nearly 600 users, just under half knew that these sleeping pills could lead to next morning drowsiness and driving impairment, and only 16% knew that women have extra susceptibility to harm. Nearly two-thirds of respondents were women, and women were less likely than men to know of increased risks. These results were consistent with an earlier in-depth interview study of 40 patients taking these sleeping pills, in which none could name the main risks highlighted in the advisories, and just one of 15 interviewed women knew of increased risks for women.[4]

Kesselheim et al. also asked about users about their intended actions in response to safety warnings.[5] Most (70%) would try to learn about other ways to help them sleep, but 61% of eszopiclone and 49% of zolpidem users said they would continue use as previously. Fewer than half intended to take a lower dose in response to safety concerns: 44% in total, including 30% of eszopiclone and 58% of zolpidem users. Thus not only was awareness limited; many saw no need to shift use. Over two-thirds of eszopiclone and three fourths of zolpidem users were taking the high doses the FDA cautioned against, and use was often long-term.

This study is part of a larger FDA-sponsored research program assessing the impact of drug safety communications for zolpidem.[6] An interrupted time series analysis found no difference in prescribing trends linked to timing of advisories, but patients received lower doses post-advisory, although the overall average dose decreased only slightly, from 9.7mg to 9.4mg/day.[7] An earlier systematic review of the impact of U.S. safety advisories found inconsistent effects.[8] A Dutch study of 46 drugs that were subject to safety advisories found long-term reductions in use for 27%; factors associated with reduced prescribing included the availability of other options, limited medical need for the drug in question, and/or severity of the adverse effect.[9]

The current case study involves one condition, insomnia, and might not be generalizable. However, a basic tenet of risk communication on medicines is that how mild or serious the condition is affects users' willingness to risk harm.[10] Sleep problems are common and often transient, and in this sample 79% of users

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had no diagnosed sleep disorder.[11] Both zolpidem and eszopiclone were among the top five drugs advertised to the U.S. public in 1997 and 2004 (zolpidem) and 2012 (eszopiclone).[12] The ubiquitous nature of this advertising and the message that the promoted pill is a simple, highly effective solution to sleep problems led the non-profit group Community Catalyst to award both companies the "Bitter Pill" in 2006, "for overmarketing insomnia medications to anyone who has ever had a Bad Night's sleep."[13]

In this case, clinical trials indicate modest effects of the drugs. A systematic review of trial data submitted to the FDA for approval of eszopiclone, zolpidem and a third drug, zaleplon, found only small differences between drug and placebo: 6 minutes for patients' impressions of sleep latency (time needed to get to sleep), and 22 minutes difference in polysomnographic sleep latency.[14] Most trials were manufacturer-sponsored and initiated. A Cochrane systematic review found that eszopiclone shortened sleep latency on average by 15.2 minutes [95% CI -20.8, -9.6] in sponsor-initiated trials but only 8.3 minutes [95% CI -14.2, -2.3] in investigator-initiated trials, and in the latter (n=676 patients), total sleep time did not differ significantly between drug and placebo.[15] Differences linked to sponsorship were not statistically significant, but the direction of effect is consistent with a sponsorship bias.[16]

The UK National Institute of Health and Care Excellence (NICE) recommends hypnotic use only for severe insomnia, at low doses and for short periods.[17] NICE's assessment of zolpidem and zopiclone — a sedative/hypnotic that is available in Europe — recommends against first-line use if drugs are needed because of lack of compelling evidence of "a clinically useful difference ... from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse," compared with less costly short acting benzodiazepines.[18] (Eszopiclone is the stereoisomer of zopiclone, with largely similar effects.[19])

Regulatory warnings on harm rarely address limits to evidence of benefit, although this is an important backdrop to patients' ability to translate warnings into decision-making. Varied impressions of benefit may help explain the range of intended actions in this survey.[20] The survey provides valuable insight into limits to user awareness of key safety concerns. The FDA's sponsorship of this research and a European Medicines Agency initiative to evaluate safety warnings[21] are welcome steps towards better targeting of these warnings to user needs.

In April 2019, the FDA issued another safety warning for zolpidem, eszopiclone, and zaleplon on serious injuries and deaths due to sleepwalking.[22] How users will respond is an open question not only about this warning but also cumulative evidence of harm.

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Note

The author has no conflicts to disclose.

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