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I petitioned the FDA to restrict hypnotics: here is why

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To the Editor,

After we presented data in 2012 showing that patients taking popular hypnotics suffered a four-fold increase in mortality [1], the U.S. Food and Drug Administration (FDA) wrote me, "We conclude that current evidence available for these drugs continues to support our determination that they are safe and effective for insomnia." Our mortality results were then closely replicated in 2014 among over 100,000 British general practice patients [2]. Indeed, since 2012, there have been more than 50 papers with remarkable new evidence of the risks of hypnotics.

The FDA soon realized that the most popular generic and brand hypnotics (zolpidem and eszopiclone) were NOT safe in the recommended doses that had been approved [3]. Indeed, at this writing, there have been 34 epidemiologic studies of hypnotics mortality risks, of which 33 found hypnotics associated with increased mortality ($P < 0.000001$) [4]. One small study demonstrated no general mortality risk, only a cancer mortality risk. There have been several new studies documenting that hypnotic use predicts cancer incidence and cancer deaths, several new studies documenting an association of hypnotic use with serious infections including lethal pneumonia, and a whole-nation-representative study documenting association of short-term use of hypnotics such as zolpidem with a 22.3-fold increased hazard of acute respiratory failure and a 7.41-fold increase in cardiopulmonary arrest among patients with chronic obstructive pulmonary disease (COPD) ([5] and see [supplement](#).) A recent analysis found that among U.S. men ages 45-54, overall mortality has been increasing. The authors attributed this increasing mortality mainly to suicides including ingestion deaths related to opiates [6]. In many ingestion deaths related to opiates, hypnotics are involved, and hypnotics are associated with increased opiate risk

[7,8]. There is considerable individual variation depending on genetic factors, obesity, COPD, and concomitant drugs.

The lead manufacturer of zolpidem argued that the FDA's currently-recommended starting dose is NOT effective and admitted that zolpidem causes infections [9]. Indeed, other analyses confirmed that neither zolpidem nor eszopiclone were effective in the low doses now recommended. The most authoritative NIH-sponsored meta-analysis concluded that "Z" hypnotics do not significantly increase polysomnographic total sleep time, even though much higher doses were included in that meta-analysis [10]. There seem to be no controlled trials with evidence that any U.S.-licensed hypnotic ever objectively improved any aspect of insomnia patients' daytime function or any aspect of general health. Please let us know if anybody can find such evidence. There are adequate new publications documenting that hypnotics impair objective daytime performance, as has been known for decades.

It is a mystery why hypnotics are usually prescribed. According to the U.S. National Ambulatory Medical Care Survey, insomnia was a stated reason for a patient's visit in less than a quarter of office visits where a hypnotic was prescribed, and 35% received no sleep diagnosis of any sort [11]. Moreover, the prescriptions for hypnotics must have usually been contraindicated, since no more than 10% of the women were prescribed the recommended lower doses, 22% of sustained zolpidem users were also sustained users of opioids, 23% were sustained users of a second sedative, and 34% of sustained users were depressed (as indicated by antidepressant use) [12].

The FDA has not responded to the new evidence. Hypnotics still carry no warnings about mortality or cancer risks. Perhaps, despite the strong preponderance of evidence [4], the

FDA needs more iron-clad proof from randomized placebo-controlled trials before it can protect the public.

Therefore, I have petitioned the Commissioner of the FDA to require phase IV controlled trials including vulnerable patients, of sufficient design and magnitude to demonstrate with 95% confidence whether hypnotics are free from excessive mortality risks. The manufacturers may decline to conduct such trials, which may raise questions about their confidence in the safety of their products. In any case there are unquestionably strong risks associated with hypnotic use, including increasing mortality and risk of infections. To prove the causality, however, rigorous studies as suggested above need to be done. Until then, such hypnotics should be compassionately restricted to hospice care.

Please see [supplement](#): “Petition to the FDA regarding hypnotic drugs” for further elaboration of my reasoning for restricting hypnotic use.

References

- [1] Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012;2:e000850.
- [2] Weich S, Pearce HL, Croft P, Singh S, Crome I, Bashford J, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *BMJ* 2014;348:g1996.
- [3] Farkas RH, Unger EF, Temple R. Zolpidem and Driving Impairment - Identifying Persons at Risk. *N Engl J Med* 2013;369:689-91.
- [4] Kripke DF. Mortality risk of hypnotics: strengths and limits of evidence. *Drug Saf.* Epub ahead of print, DOI 10.1007/s40264-015-0362-0, 2015.
- [5] Chung WS, Lai CY, Lin CL, Kao CH. Adverse Respiratory Events Associated With Hypnotics Use in Patients of Chronic Obstructive Pulmonary Disease: A Population-Based Case-Control Study. *Medicine (Baltimore)* 2015;94:e1110.
- [6] Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *PNAS*. 2015(Early Edition).
www.pnas.org/cgi/doi/10.1073/pnas.1518393112
- [7] Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract* 2014;27:5-16.

- [8] Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ* 2015;350:h2698.
- [9] Farkas R. Center for Drug Evaluation and Research Approval Package for: Application Number: 019908Orig1s032s034 021774Orig1s013s015. Silver Spring, MD, FDA, 2013. Accessed December 5, 2015 at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/019908Orig1s032,s034,021774Orig1s013,s015review.pdf
- [10] Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: A meta-analysis of RCTs. *J Gen Intern Med* 2007;22:1335-50.
- [11] Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in Outpatient Visits for Insomnia, Sleep Apnea, and Prescriptions for Sleep Medications among US Adults: Findings from the National Ambulatory Medical Care Survey 1999-2010. *Sleep* 2014;37:1283-93.
- [12] Moore TJ. ISMP Quarter Watch: Monitoring FDA MedWatch Reports. Philadelphia, PA, ISMP. Quarter Watch. Accessed 2015.