MAYO CLINIC

ORIGINAL ARTICLE

Insomnia From Drug Treatments: Evidence From Meta-analyses of Randomized Trials and Concordance With Prescribing Information

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Abstract

Objective: To determine whether drugs used to treat diverse conditions cause insomnia symptoms and whether their prescription information is concordant with this evidence.

Methods: We conducted a survey of meta-analyses (Cochrane Database of Systematic Reviews) and comparisons with package inserts compiled in the *Physicians' Desk Reference* (*PDR*). We identified randomized controlled trials (RCTs) in which any drug had been evaluated vs placebo and sleep had been assessed. We collectively referred to insomnia-related outcomes as *sleep disturbance*. We also searched the *PDR* to identify any insomnia symptoms listed for drugs with RCT evidence available.

Results: Seventy-four Cochrane systematic reviews corresponding to 274 RCTs assessed 88 drugs in 27 different conditions, providing evidence on 109 drug-condition pairs. Of these 88 drugs, 5 decreased sleep problems and 19 increased sleep problems; 64 drugs had no nominally statistically significant effect on sleep. Acetylcholinesterase inhibitors, dopamine agonists, and selective serotonin reuptake inhibitors were the drug classes most importantly associated with sleep disturbance. Of 35 drugs that included disturbed sleep as an adverse effect in the *PDR*, only 14 had RCT evidence supporting such effect, and 2 had evidence of increasing and decreasing sleep problems in RCTs, although this was not shown in the *PDR*. We identified weak concordance between the *PDR* and RCTs (weighted κ=0.31; $P<.001$).

Conclusion: The RCTs offer substantial evidence about the common effects of drugs on the risk of sleep disturbance; currently, prescription information only partially agrees with the available randomized evidence.

 ■ Mayo Clin Proc. 2016;■■(■):1-16

Impaired sleep is a major, yet unmet, public health challenge associated with enormous economic and societal cost.[1-5] Population-based surveys estimate that 35% to 50% of adults report symptoms of insomnia, such as difficulty initiating or maintaining sleep and associated daytime impairment,[6-8] whereas the prevalence of insomnia disorder, defined by stringent diagnostic criteria,[9] ranges from 12% to 20%.[10-12] Although disturbed sleep can be a symptom or an independent disorder (insomnia), it is most frequently encountered as a comorbid condition with another medical or psychiatric disease[11-14] and has been identified as a risk factor for chronic mental[15,16] and physical[10,17,18] illnesses. In that context, it is important to recognize that many drugs used to treat diverse clinical conditions may adversely affect the quality and duration of sleep.[19] Some drugs may improve sleep, whereas many others may disturb sleep and cause insomnia symptoms or aggravate insomnia. This effect needs to be heavily considered in recommending a specific drug or class of drugs for diverse indications and in specific patients, especially in the face of evidence showing that treating the sleep disturbance and the comorbid condition simultaneously may improve the comorbid condition more than treating it alone.[3,20]

Regulatory-approved package inserts, such as those compiled in the *Physicians' Desk Reference* (*PDR*) in the United States, are supposed to list adverse effects systematically, and this

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should ideally include insomnia. However, information in these established reference sources is often compiled nonsystematically, with subjective interpretation of the results from various clinical trials. This does not have to be the case because evidence from randomized controlled trials (RCTs) on the occurrence of insomnia symptoms with specific drugs or classes of drugs in various settings can be evaluated quantitatively and results can be synthesized in meta-analyses[21-23] whenever several different trials exist on the same drug and indication.

The Cochrane Database of Systematic Reviews (CDSR) has already published more than 6000 systematic reviews that cumulatively encompass most randomized evidence on medical interventions. It is possible to peruse the CDSR systematically and identify all the RCTs and meta-analyses that examine disturbed sleep and related outcomes. Important questions can be asked: How commonly do RCTs and meta-analyses find evidence of increased (or decreased) risk of sleep disturbance with specific drugs and classes of drugs? Do the results of RCTs and their meta-analyses concord with the statements made in regulatory drug reference sources, such as package inserts? Answering these questions using large-scale assessment of multiple drugs would help elucidate the effect of drugs on sleep and would allow for the evaluation of widely used reference sources regarding their coverage of this important health outcome.

METHODS

Eligibility Criteria

We considered Cochrane systematic reviews including binary or continuous data on sleep-related outcomes during follow-up for the comparison of an experimental treatment with placebo. Comparisons were included regardless of the number of trials with data for each outcome. Comparisons were also accepted for any disease or condition. Protocols were excluded, as were reviews in which the assessed outcomes did not include at least 1 sleep-related outcome. Reviews were accepted regardless of whether the sleep-related assessments pertained to the evaluation of outcome status or change (improvement or deterioration).

Search Strategy and Outcome Definition

Using a broad search to ensure that all eligible outcomes were captured, we searched the CDSR (2012, issue 8; last search performed August 31, 2012) using the terms *sleep*, *insomnia*, *sleeplessness*, *hypersomnia*, and *dreams*. Reviews containing more than 1 eligible comparison were considered separately. Somnolence, drowsiness, sedation, abnormal dreams, and hypersomnia were excluded as outcomes because they refer to alterations of wake function and state of consciousness rather than directly to sleep disturbance mainly defined by inability to initiate or maintain sleep.

Eligible sleep-related outcomes included insomnia, sleep disruption, sleep problems, and sleep disturbance, as well as related continuous scale outcomes (self-assessed sleep quality, awakenings, sleep latency, and inability to sleep) (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). In these analyses, we collectively refer to these outcomes as *sleep disturbance*.

We focused on drugs, including biological agents and immune therapies, but excluded vitamins and supplements as well as other types of interventions (surgical devices and psychological, behavioral, social, cognitive, and other nondrug interventions). Meta-analyses were accepted regardless of whether they included trials on a single drug or several different drugs belonging to the same class.

To avoid the use of duplicate or overlapping information, we used the following rules: When assessments for sleep were performed at several different time points, we retained the data for the time point with the largest number of studies (or smaller standard error when different time points had the same number of studies). When analyses with different definitions of eligible insomnia outcomes were found, we selected the one with the smaller standard error in the meta-analysis of all trials. When meta-analyses were available for separate subgroups and for the combination of subgroups, we retained only the latter. Conversely, when separate meta-analyses had been performed on different trials for the same drug and condition but for different definitions of otherwise eligible outcomes (eg, cabergoline had 2 trials with data on