Waking up to sleeping pill risks

March 11 2020, by Lane McKenna

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Insomnia is a real medical issue. But is it so prevalent that millions of Americans need to take sleeping pills every night?

Leading medical professionals are becoming increasingly concerned that those of us now taking sleeping pills face greater risks of long-term

dependence and a laundry list of other medical problems, oftentimes outweighing the limited sleep benefits the drugs provide. And yet, physicians continue to prescribe sleeping pills—even the highly disregarded "benzo" drugs—to millions of people. To better understand this dilemma, we spoke with Anna Lembke, MD, associate professor and chief of addiction medicine at Stanford University School of Medicine.

Is insomnia really all that serious?

Insomnia disorder is defined in the International Classification of Sleep Disorders (3rd Edition) as a complaint of trouble initiating or maintaining sleep which is associated with day-time consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep. When this problem lasts for less than three months, it is considered short-term insomnia—which affects an estimated 30-50% of the population. When the condition persists longer than three months, at a frequency of at least three times/week, it is called chronic insomnia—which affects an estimated 5-10% of the population.

As summarized in the 2017 American Academy of Sleep Medicine (AASM) Clinical Practice Guideline: Insomnia, chronic insomnia is associated with numerous adverse effects, including:

- Marked impairment in functional status
- Increased rates of work absenteeism
- Higher rates of occupational and motor vehicle accidents
- Higher risk of developing psychiatric disorders, especially mood disorders
- Increased risk of relapse for depression and alcoholism
- Increased risk for cardiovascular disease

As Dr. Anna Lembke concludes: "Insomnia is a real problem." However,

she goes on to assert that it's a "self-caused" one:

"Nothing is different about our brains now than 150 years ago. The problem is our lifestyle and how we interface with technology, all of which conspire to keep us up well past the time we should be going to bed…. not to mention the fact that most of us don't get enough exercise…. so our bodies aren't worn out, even though our brains are. The way to help this problem is not to take more pills, but to change the way we live."

Current insomnia treatments: Pills rule

In an attempt to cope with insomnia, pills have become the primary strategy adopted by most physicians and eagerly adhered to by a willing-to-believe population of folks seeking a better sleep ritual—despite compelling medical research showing greater benefits from non-pharmaceutical treatments. In fact, a staggering 1 in 4 (or more) Americans "take something" to help them sleep. When we asked Dr. Lembke how this percentage could be so high, her response was simple but eye-opening: "We're a culture that has come to rely on pills as a quick fix to our problems."

According to the 2015 National Sleep Foundation Survey, 29% of Americans regularly take pills to sleep, at least several times each month, broken down into these four categories:

- 7% prescription drugs
- 9% over-the-counter drug aids
- 11% alcohol
- 2% melatonin

Prescription sleep medications have soared in

popularity

Let's briefly look at the first category of substances, taken by 7% of us as sleep aids: drugs that physicians prescribe. Most of them fall into these five groups: (1) benzodiazepine sedative-hypnotics (BZDs or "benzos") such as temazepam (Restoril); (2) non-benzodiazepine sedative-hypnotics (non-BZDs, BzRAs or "Z-drugs") such as zolpidem (Ambien); (3) antidepressants such as trazadone; (4) newer drugs that target the sleep-cycle without hypnotic properties, such as ramelteon; and (5) some older drugs approved for indications other than insomnia, but prescribed "off-label" as sleep aids, such as gabapentin.

Benzos: Risky and overprescribed

Benzodiazepines ("benzos," BZDs) are sedative-hypnotic drugs that produce central nervous system (CNS) depression by enhancing the effects of the major inhibitory neurotransmitter (gammaaminobutyric acid), thereby decreasing brain activity. These "controlled substances" include flurazepam, quazepam (Doral), temazepam (Restoril and generic), triazolam (Halcion and generic), alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium) and lorazepam (Ativan). Many benzos are approved for the treatment of mental disorders such as anxiety—but they are prescribed "off-label" just for insomnia nevertheless.

A 2018 Journal of Clinical Medicine review article summarizes the rather tragic trajectory these drugs have taken [our emphasis added]:

"After their introduction in the early 1960s, BZDs quickly became the most common 'minor tranquilizer," replacing older agents such as barbiturates. Many prescribers were led to believe that BZDs were harmless and had no dependence risk, so BZDs were prescribed

frequently and often long-term for various conditions: anxiety, insomnia, substance withdrawal, anesthesia, muscle tension, seizures, psychosis, and depression, among other indications. By the 1970s, BZDs were the most commonly prescribed medications in the world. Unfortunately, the potential for abuse and dependence was rapidly discovered."

In 1975, BZDs were placed on the Food and Drug Administration (FDA) restricted drug list, reflecting growing concerns about misuse. In 1990, the American Psychiatric Association (APA) officially recognized the risk of BZD dependence, and in the years that followed dozens of research studies showed the growing data and warnings about BZDs. Still, as the J. Clin. Med. reviewers note:

"Despite recommendations against long-term BZD use (i.e., more than 2–4 weeks), many providers continue to prescribe them for months or even years, allowing for dependence and diversion to occur…. Total BZD use actually increased from 1999 to 2014, largely driven by increases in long-term use. About 15% of the U.S. population take BZDs in any given year and about 6% of the U.S. population have abused sedative-hypnotics… drugs that—unlike cannabis, amphetamines and opioids—exclusively originate from the medical system."

Sensing that the medical system was, indeed, turning a blind eye to the dangers of BZD prescribing patterns in the U.S., Dr. Lembke and two other authors wrote a 2018 Perspective: "Our Other Prescription Drug Problem" that was published in the *New England Journal of Medicine*, which included this stern observation:

"Despite the many parallels to the opioid epidemic, there has been little discussion in the media or among clinicians, policymakers, and educators about the problem of overprescribing and overuse of benzodiazepines and z-drugs, or about the harm attributable to these drugs and their illicit analogues. We believe national efforts to reduce

overprescribing of opioids and to educate the medical and lay communities about their risks should be expanded to target benzodiazepines."

While the above statement may sound dramatic—comparing benzo prescribing to the opioid epidemic—so should it, as there are some real parallels. As the authors explain, "benzodiazepines have proven utility when they are used intermittently and for less than 1 month at a time. But when they are used daily and for extended periods, the benefits of benzodiazepines diminish and the risks associated with their use increase. Many prescribers don't realize that benzodiazepines can be addictive and when taken daily can worsen anxiety, contribute to persistent insomnia, and cause death. Other risks associated with benzodiazepines include cognitive decline, accidental injuries and falls, and increased rates of hospital admission and emergency department visits."

Lembke elaborated further on the dangers of benzos in our recent interview:

"Benzodiazepines cause tolerance, meaning we need more over time to get the same effect; and dependence, meaning that if we cut back or stop, we get rebound symptoms: more anxiety, more insomnia. Therefore, they're not a good long-term drug. Also, the longer we take them, the more likely we are to get addicted to them, making it that much harder to stop. Finally, benzodiazepines can kill, especially when combined with other sedating drugs like opioids or alcohol."

The medical research on benzos, both from an efficacy and a safety viewpoint, is highly critical: As the 2018 *J. Clin. Med.* review article summarizes, quite simply "there are no studies to support the long-term use of BZDs for insomnia, and the evidence that is supportive of short-term use is based on very few studies." A Canadian meta-analysis of

benzodiazepine use unequivocally states:

"It is clear that benzodiazepines do not provide a major advantage over placebo and that they are are not free of adverse effects. In light of the strength of the placebo effect in patients with insomnia, physicians and patients who believe that benzodiazepines are highly effective may wish to reconsider their treatment choice. None of the data extracted in this review support long-term use (i.e., longer than two weeks)."

So why are benzos still so heavily prescribed?

The answer is as difficult to explain as it is to understand and accept. But several factors point, to put it bluntly, to the power of addiction:

"Like alcohol, the sedating properties of BZDs often deceive patients into thinking that BZDs improve sleep when, in actuality, they tend to induce the early stages of sleep while inhibiting the deep, most restorative, stages of sleep" (2018 J. Clin. Med. review article).

In other words, patients report that the drugs are "helping"—not because of objective, measurable data, but rather based on patient "reporting" driven by the desire (read: addiction) to keep taking these drugs. The Canadian meta-analysis explains:

"Patients taking benzodiazepines tended to overestimate sleep outcome measures and the efficacy of their medication.… [Although] benzodiazepines were associated with more reports of adverse effects including drowsiness, dizziness or lightheadedness and cognitive impairment, this did not translate into higher discontinuation rates. Rebound insomnia associated with the abrupt withdrawal of benzodiazepine treatment is another factor likely to promote continuance of the drug."

Benzos are often prescribed as a front-line treatment for certain mental conditions, like anxiety (that often co-exist with insomnia), because they work more rapidly than do certain antidepressants. Thus, it's easy to envision how entire population subsets like those with mental health conditions can get "hooked" into the addictive benzo pattern. However, "despite many clinicians intending to taper/discontinue BZDs after the 4–6 weeks it takes SSRIs [antidepressants] to have their therapeutic effect, 12% of patients receiving this regiment continue BZDs for over 6 months—sometimes in the absence of SSRIs—likely indicating the difficulty of discontinuing BZDs once started. Despite the absence of efficacy and the evidence of risks, the rate of physicians prescribing this way almost doubled between 2001 and 2014."

Thus, it is likely that physicians may overprescribe benzos because they succumb to the addictive pressures brought to bear by their patients, coupled with a failure to heed the evidence from newer medical studies that show this very problem as well as the many other medical risks inherent in long-term use of benzos. As a 2016 Mayo Clinic Proceedings review article states:

"There are several interdependent reasons why doctors are unable to change their benzodiazepine prescription patterns. Some are intrinsic to physicians, including insufficient recognition of adverse effects, conviction that the risk to benefit ratio favors the latter, perceived lack of skills and training on how to respond to problems that occur during a taper, resource constraints such as limited time and a resultant decision to focus on other important medical issues in this population, fear of jeopardizing the doctor-patient relationship or fear of pushback leading to patients finding other doctors, unwillingness to question other colleagues' prescription rationales, and opinion that discontinuation could be too stressful for an elderly user with a limited life expectancy."

Similarly, the 2017 AASM Clinical Practice Guideline notes that when

physicians are surveyed, they "note a lack of awareness and/or availability of alternative treatments. Many favor an initial approach of treating associated comorbidities and advising good sleep hygiene…. [but] an ever-increasing amount of data makes it clear that the latter approach is very often unsuccessful, leaving providers feeling compelled to prescribe medications. Most of those surveyed recognize the need for additional, non-pharmacological treatment for their patients, but cite a number of barriers to acquiring such treatment."

The Mayo Clinic article also notes that other reasons for the "massively prescribed" benzodiazepines are external to physicians: "patients' resistance to change, health systems with insufficient reimbursement for the invested time and effort, limited availability of psychotherapists, absence of scheduled medication reviews, or inability to access support from psychiatrists in a timely fashion."

Enter Ambien and other "Z-drugs"

Non-benzodiazepine hypnotics (non-BZDs, or BzRAs, or "Z-drugs") are hypnotic substances that, like benzos, target the GABA-A receptors in the brain. Z-drugs, however, are synthesized so that the drugs have a shorter half-life (two hours or less), suggesting that withdrawal after discontinuing these drugs is minimized (unless they are abused or taken in high doses for an extended period)—making them, ostensibly, "safer" than benzos if prescribed and used appropriately. These so-called Z-drugs first became widely available in the U.S. in the 1990s. They include zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)—the most widely used prescription hypnotic medication and the fourth most frequently prescribed psychiatric drug (2013 data); zaleplon (Sonata); and eszopiclone (Lunesta).

An astounding 3.8 million adults aged 18 to 85 years reported 1 or more prescriptions for zolpidem (Ambien and generic equivalents) in 2015,

according to the U.S. Medical Expenditure Panel Survey (MEPS) for 2015, as reported in a 2018 *JAMA Internal Medicine* research letter.

The 2017 AASM Clinical Practice Guideline, which reviewed every relevant and worthwhile clinical study to date of Z-drugs, concluded that, if used "appropriately" (for those intending to sleep 8 hours), Z-drugs like Ambien have "benefits deemed to marginally outweigh harms." However, the panel could only give Ambien and the other Z-drugs a "Weak" recommendation.

When we asked Dr. Lembke where she stands on the Z-drugs for insomnia, she stated:

"Z-drugs like Ambien work on the same receptor complex as benzodiazepines and alcohol, meaning they pose similar risks. They lead to tolerance and dependence if taken daily for longer stretches of time (1-2 weeks or more). They are potentially addictive. They can kill. These medications were never intended for daily or long-term use, although they're often prescribed and taken that way."

We asked Dr. Lembke why some clinical studies fail to show the Z-drug risks that she and other physicians and researchers warn of. Her response:

"The studies looking at these drugs don't follow patients longer that about 12 weeks, and most studies are much shorter (1-2 weeks). In real-world clinical care, I get to see the effects of Z-drugs on patients taking them for months and years. So clinical care is a better source of data for long term outcomes. In the long term, for some patients (there is inter-individual variability with all drugs), Z-drugs are just as addictive and just as potentially lethal as benzodiazepines such as Xanax. This is particularly true for older people who have lost the brain plasticity to re-adjust to not taking the drug."

Lembke is not alone in her concerns about Z-drug risks. A British Association for Psychopharmacology (BAP) consensus statement called the adverse effects of Z-drugs "comparable with benzodiazepines." Research published in the *British Journal of Clinical Pharmacology* indicates that the consequences of Ambien misuse meet some of the most important criteria of chemical dependency, including:

- Tolerance, or the need for higher doses of Ambien in order to achieve the same results
- Withdrawal, or the presence of uncomfortable physical and psychological reactions to the sudden discontinuation of the drug
- Compulsive use, or a preoccupation with using the medication in spite of its negative consequences on health, job performance, or relationships
- Manipulative or unethical behavior, such as drug-seeking, forging prescriptions, or faking symptoms in order to obtain more of the drug

In conclusion, the authors stated that "this study adds to the growing evidence that zolpidem has the potential for abuse and dependence." As a consequence of the British report, the French drug monograph was modified by the French Health Authorities to include this sentence: "Pharmacodependence may develop even at therapeutic doses, and/or for patients who do not show an individualized risk factor."

Similarly, a 2018 *JAMA Intern Med.* research letter comes to a striking conclusion:

"Optimal safe use of zolpidem is uncommon. Although efficacy declines substantially after 14 days of continuous administration, most zolpidem patients reported sustained use, with increased risk of dependence, given that zolpidem is a class IV controlled substance. Overdose and next-day impairment risks were increased with the 41.4% combining zolpidem

with sustained use of other CNS-depressant drugs."

Likewise, Lembke remarks that she "has had many patients over the years addicted to Ambien."

In a 2018 Progress in Neurology and Psychiatry review article, researchers concluded that "therapeutic doses of zopiclone have a high risk of psychomotor and cognitive impairment, poor mental alertness and poor motor coordination, within 12 hours of administration. The risk of hangover effects with zopiclone is comparable or less than short-acting benzodiazepines. Zolpidem can, dose-dependently, impair word recall and recognition 6–8 hours post-administration after which the risk is reduced. Zaleplon may cause significant, dose-independent psychomotor impairment immediately after administration, but not the next day, or during the night."

Ambien and Z-drugs: No longer recommended for older adults

Other organizations, such as the American Geriatrics Society (AGS), warn of Ambien's risks/dangers and relative "minimal improvements in sleep latency and duration." In 2015, the AGS Beers Criteria (which has since undergone a 2019 update) was published, and in it the expert panel stated that "nonbenzodiazepines are not recommended for chronic use," especially in older populations, because such use leads to greater risk of falls, hip fractures and other accidents.

The 2016 *Mayo Clinic Proceedings* study summed it up well:

"An important update in the new criteria [2015 Beers Criteria] is that nonbenzodiazepine receptor agonists (such as eszopiclone, zalpelon, and zolpidem) are unambiguously to be avoided regardless of duration of

use, whereas the 2012 recommendations were more permissive of their use. These drugs possess minimal efficacy in treating insomnia beyond acute periods measured in days and considerably increase the risk of adverse effects, including delirium, falls, fractures, and motor vehicle accidents."

Similarly, a 2016 Clinical Therapeutics study concludes: "Although non-BzRAs have improved safety profiles compared with benzodiazepines, their side effects include dementia, serious injury, and fractures, which should limit their use."

Is the FDA doing anything about it?

In 2013, the U.S. Food and Drug Administration (FDA) issued a report concerning the risk of next-morning impairment after use of insomnia drugs, and in that report FDA required lower recommended doses for certain drugs containing Ambien. In that same year, FDA approved new label changes and dosing for zolpidem (Ambien) products, and a recommendation to avoid driving the day after using Ambien CR. In April 2019, FDA issued a warning about the risk known as "complex sleep behavior," which can occur as a result of taking Z-drugs. Examples of this condition, in which "you are asleep or not fully awake," include sleepwalking, sleep driving, sleep cooking, or taking other medicines:

"FDA has received reports of people taking these insomnia medicines and accidentally overdosing, falling, being burned, shooting themselves, and wandering outside in extremely cold weather, among other incidents."

Because of these incidents, in 2019 FDA added a Boxed Warning—FDA's most prominent warning—to the prescribing information, known as "labeling," and patient Medication Guides of Ambien and similar drugs. In addition, FDA added a contraindication,

which is the agency's strongest warning, stating that patients who have experienced an episode of what is known as complex sleep behavior should not take these drugs.

We asked Dr. Lembke whether she would prefer that physicians refrain completely from prescribing benzos or Z-drugs: ""It's not that I wished no one was taking benzos or Z-drugs. They're important and useful tools when used appropriately. The problem is that too many people are taking them daily for long periods of time, which is not how they should be used."

Withdrawing from sleeping pills: Watch out

So, having read all of the above, some readers may be about to curtail taking sleeping pills. But read this first:

Withdrawal, one of the hallmark signs of drug addiction, has been observed in long-term Ambien users. People who have become accustomed to taking high doses of Ambien often feel anxious, restless, agitated, shaky, and tired when they attempt to quit the drug too quickly. Nausea, vomiting, delirium, and seizure activity have also been reported.

According to a Harvard Health Publications report, rebound insomnia typically arises after stopping sleeping pills abruptly, and it is usually worse than the initial insomnia that led to taking sleeping pills in the first place. The severity and duration of withdrawal symptoms vary from person to person, and there is no way to predict how the body will react without nonbenzodiazepine hypnotics in its system.

Because complications could arise, it is best to stop taking sleeping aids with the help of a qualified healthcare provider. According to Dr. Lembke, "The answer is a slow taper. My clinic now has many patients who come specifically for help tapering off of benzos and other similar

drugs. The taper process can take years for patients who have been on the drugs for years."

Antidepressants: Possibly safer, but limited data

The tricyclic antidepressant, doxepin (Silenor and generic), was approved by the FDA in March 2010 for the treatment of anxiety, depression and also for insomnia. As such, it is only the second insomnia medication not designated as a controlled substance. Mayo Clinic opines:

"The antidepressants doxepin and mirtazapine may be good options for treating insomnia in elderly patients. Doxepin is an FDA-approved medication for insomnia, and the AGS criteria permit the use of doxepin at dosages of less than 6 mg/d in older patients. At such ultralow doses, doxepin is purported to be highly selective for H1 receptors, to lack anticholinergic effects, and to induce sleep effectively. In our opinion, prescribers should continue to exert caution and monitor for anticholinergic effects even with ultralow doxepin doses, particularly when prescribed to fragile older patients."

Trazodone is also increasingly prescribed for insomnia indications, although there are few large studies of its use for this indication and it is not FDA-approved as such. Mayo Clinic, however, warns that, "Trazodone, a sedating antidepressant, can cause orthostasis and lacks evidence for sustained efficacy in treating insomnia." The AASM Clinical Guideline would not recommend trazodone, citing "the absence of significant efficacy for trazodone 50 mg and the paucity of information regarding harms," although the task force did state that trazodone is perceived as a "safer" sleep-promoting agent by many physicians.

In her *NEJM* article, Lembke mentions that "there are safer treatment alternatives for anxiety and insomnia, including selective serotonin-

reuptake inhibitors and behavioral interventions. We asked her to comment further:

"We use the SSRIs, the tricyclics, and trazodone most commonly when we absolutely need to prescribe a medication to help people sleep. These medications tend not to be addictive, and the risk benefit ratio is better than with benzos. These drugs are less problematic because patients don't typically build up tolerance and become dependent, so they're safer. But every drug comes with side effects."

"In clinical care, I prefer antidepressants to benzodiazepines, because they are not usually addictive and can be stopped relatively easily. But as above, every drug has side effects. The best long-term interventions for insomnia are behavioral: exercise, a healthy diet, good sleep hygiene, mind-body practices, etc."

Newer medications: Promising, but more studies needed

Ramelteon (Rozerem), the other hypnotic that is not a controlled substance, is a melatonin-agonist, a hormone that helps to regulate the body's circadian cycles. Suvorexant (Belsomra) is an orexin receptor antagonist.

While some of these newer meds show promise, Lembke warns that, "Any new sleep medicine should be viewed with caution. It may have serious side effects that didn't emerge in FDA-approval trials, especially the risk of addiction, which can take longer to develop and is hard to detect because of social desirability bias."

Off-label prescriptions: Uncertain risks, uncertain benefits

Older drugs approved for indications other than insomnia are also prescribed "off-label" as sleep aids. (In fact, most of the BZDs, or benzos, listed in #1, are also prescribed "off-label," as they are approved for anxiety or other indications, rather than for insomnia specifically.) There are too many to name, but they include adrenergic inhibitors (e.g., propranolol, prazosin, clonidine, guanfacine), antihistamines (e.g., hydroxyzine, diphenhydramine), anticonvulsants (e.g., gabapentin, pregabalin, lamotrigine, topiramate, valproate), and antipsychotics (e.g., quetiapine, olanzapine, risperidone).

Lembke warns that gabapentin (widely used for the treatment of epilepsy, neuropathic pain, and restless legs syndrome, but also commonly prescribed for insomnia) "has the potential to be addictive and causes weight gain."

OTC sleep aids: Minimal efficacy and not without risks

Most over-the-counter sleep aids, including Nytol and Sominex, contain the antihistamine diphenhydramine. A few, such as Unisom SleepTabs, contain doxylamine. Aspirin-Free Anacin PM and Extra Strength Tylenol PM combine antihistamines with the pain reliever acetaminophen.

The antihistamines can pose cognitive side effects, especially for older people. Furthermore, there is no information about the safety of taking such medications over the long term. Alcohol heightens the effect of over-the-counter sleep medications, which can also interact adversely with some other drugs.

As the AASM Clinical Guideline states:

"Unfortunately, many individuals use medications or substances (e.g. over-the-counter sleep aids or alcohol) which are not demonstrated to be effective in managing insomnia and/or have significant potential for harm.… significant knowledge gaps and anxieties about the proper usage of these agents exists among the prescribers."

Non-drug insomnia treatments: Better, safer

Lembke sums up her professional guidance for treating insomnia:

"Behavioral interventions are the best, and include exercise, a healthy diet, a regular sleep-wake cycle, and behavioral conditioning to associate certain cues with sleep. Technology and devices are another important point of discussion. No devices, including phones, in the bedroom, and especially not in the bed. A lot of people now sleep with their phones. [Sigh.]"

Most leading medical groups and researchers agree: The AASM Clinical Guideline points to CBT-I (cognitive behavioral therapy for insomnia) as a "standard of treatment" that carries a significantly favorable benefit:risk ratio." Cognitive behavioral therapy for insomnia incorporates sleep education, cognitive therapy, and behavioral interventions relying on sleep hygiene and sleep restriction.

Likewise, the *J. Clin. Med*. review concludes that, "For insomnia, psychological and behavioral therapies (e.g., CBT including CBT for insomnia (CBT-I), stimulus control, relaxation, sleep restriction) are the standard of care.

In May 2016, the American College of Physicians published its own clinical practice guideline for the management of chronic insomnia. This guideline also recommends that all patients with chronic insomnia receive CBT-I as the initial treatment intervention.

As the AASM Clinical Guideline authors so aptly expressed, "studies make clear that the gains associated with CBT-I are durable following completion of treatment, whereas those associated with medication tend to dissipate following discontinuation of the drug."

Or, to reiterate Dr. Lembke's bottom line:

"The way to help this problem is not to take more pills, but to change the way we live."

More information: Sateia, MJ. International Classification of Sleep Disorders—Third Edition. American Academy of Sleep Medicine, Darien, IL. 2014.

Sateia, MJ, Buysse, DJ et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine*, Vol. 13, No. 2, 2017.

2005 Adult Sleep Habits and Styles. 2015 National Sleep Foundation Survey. Published 2005.

Lembke A, Papac J, Humphreys K. Our Other Prescription Drug Problem. *N Engl J Med*. 2018; 378:693-695.

Guina J and Merrill B. Benzodiazepines I: Upping the Care on Downers. *J. Clin. Med.* 30 January 2018.

Meta-analysis of benzodiazepine use in the treatment of insomnia. *Canadian Medical Association Journal*. February 2000. 162(2):225-33.

Victorri-Vigneau C, Dailly E, Veyrac G and Jolliet P. Evidence of zolpidem abuse and dependence: results of the French Centre for

Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol.* 2007 Aug; 64(2): 198–209.

Agravat A. 'Z'-hypnotics versus benzodiazepines for the treatment of insomnia. *Progress in Neurology and Psychiatry*. Volume 22.02 April-June 2018.

American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. 2012 (and 2015 and 2019 updates).

Schroeck, JL et al. Review of Safety and Efficacy of Sleep Medicines in Older Adults. *Clinical Therapeutics*. Volume 38, Number 11, 2016.

Moore, TJ and Mattison, DR. Assessment of Patterns of Potentially Unsafe Use of Zolpidem. *JAMA Intern Med.* 2018;178(9):1275-1277.

Provided by Stanford University