NIH Panel Assesses Treatments for Insomnia

Members conclude that more studies are needed to assess new drugs and alternative therapies.

BY HEIDI SPLETE
Senior Writer

New benzodiazepine receptor agonists for chronic insomnia—zaleplon, zolpidem, and eszopiclone—have shown fewer adverse effects compared with other medications, but additional studies are needed to assess these drugs' long-term effectiveness, concluded members of an independent panel convened by the National Institutes of Health in Bethesda, Md.

Only eszopiclone (Lunesta) has been approved for the long-term treatment of insomnia; the other drugs are approved for up to 35 days of use.

Five benzodiazepines—estazolam, flurazepam, quazepam, temazepam, and triazolam—also are approved by the Food and Drug Administration to treat insomnia, but adverse events including dependence, daytime sleepiness, and lack of motor coordination are more likely with these drugs than with the new receptor agonists.

Although commonly used, all of these medications require more research.

"The real problem with these kinds of compounds is that there are very few data on their efficacy in the treatment of chronic insomnia, yet we know from other research that they produce substantial side effects," panel member Robert J. DeRubeis, Ph.D., said in an interview.

After reviewing information on the latest research and the available treatments, the panel members concluded that limited guidance and resources exist for clinicians about the treatment of chronic insomnia. They emphasized that more research is needed on the available treatment methods, which include hypnotic medications, behavioral therapy, and alternative medicine, as well as antidepressants, antihistamines, and antipsychotics.

Given the availability of treatments with demonstrated efficacy and fewer side effects in the short term, the panel could not recommend off-label use of nonapproved substances, said Dr. DeRubeis, chair of the department of psychology at the University of Pennsylvania in Philadelphia.

Antidepressants, particularly trazodone, are often prescribed off label for insomnia, but there are no data on the effects of long-term use of such agents, the panelists noted.

"Trazodone is not without danger," panel member James N. Kvale, M.D., a professor in the department of family and community medicine at the University of Texas, San Antonio, said in an interview. "It loses effectiveness as a sleep aid after 7 days, and its real value for the chronically ill person is to be questioned."

Chronic sleep loss is a public health problem associated with impaired psychomotor and cognitive function, and may contribute to the risk of falls in older adults, the panelists wrote in a draft consensus statement.

In addition, millions of Americans attempt to treat their sleep problems for prolonged periods of time with untested or off-label products including alcohol and antihistamines, despite a lack of evidence for their effectiveness.

Doctors can start by advising sleepless patients to consider environmental factors, including temperature, light, and sound in the bedroom. If problems persist, doctors should consider referring patients for cognitive-behavioral therapy before prescribing medications, Dr. Kvale said. Given the lack of evidence to support even the approved drug treatments for long-term use, it's important to explore nonpharmaceutical ways to manage sleep problems, he explained.

Cognitive-behavioral therapy (CBT) has proved successful for managing insomnia in randomized, controlled trials. Use of CBT involves training in relaxation, controlling external stimuli, and targeting anxiety-inducing beliefs about sleep and sleep loss. But few clinicians are experts in treating chronic insomnia with CBT, and these techniques are not widely used, the panelists noted.

Although CBT and benzodiazepine receptor agonists have shown benefits in patients with chronic insomnia, additional research is needed to compare the various treatments with each other, and to determine the effectiveness of the treatments across different populations.

The hormone melatonin and the herb valerian have been used for insomnia, but neither of these substances is regulated by the FDA, and the variation in content among preparations makes scientific comparison difficult.

Other alternative treatments for insomnia include light therapy, acupuncture, yoga, and tai chi, but none of these have been sufficiently evaluated, the panel said in the draft statement.

To close the gaps in knowledge, the panel recommended that future studies be randomized, controlled trials comparing at least two effective or promising treatments, including drugs, CBT, and combination therapies.

Understudied features of chronic insomnia include its effects on daytime functioning that prevent people from engaging in a productive and enjoyable work and social life, Dr. DeRubeis added.

Little is known about the incidence of chronic insomnia because it can be difficult to identify as a distinct problem, as opposed to a side effect of other conditions or medications. For example, a middle-aged woman with arthritis may have trouble sleeping, but she talks to her doctor about her arthritis without mentioning insomnia. Population-based studies suggest that about 30% of the general population complain of sleep problems, the panelists noted. ■

Compared With Trials, Warfarin Is Half as Effective at Stroke Prevention in Real World

BY MITCHEL L. ZOLER
Philadelphia Bureau

New Orleans — Real world experience with warfarin suggests that it is not as good at preventing strokes among patients with atrial fibrillation as clinical trial results suggested, especially among African Americans.

A review of more than 23,000 Medicare patients with atrial fibrillation showed that overall, warfarin prophylaxis cut the stroke rate by 34%, compared with a 65% cut in strokes that's been consistently seen in clinical trials, Brian F. Gage, M.D., reported at the 30th International Stroke Conference.

This lower efficacy is "disappointing," said Dr. Gage, an internist at Washington University in St. Louis.

But warfarin performed even worse among the African Americans in the study. In this group, warfarin use was associated with a trend toward more strokes, although this increase was not statistically significant, compared with African Americans not on warfarin.

The study used a national sample of 23,657 Medicare patients with atrial fibrillation treated during April 1998 though March 1999. Warfarin prophylaxis was used by 43% of African Americans in the study and by 50% of the white patients.

Information culled from the medical records of the patients on warfarin therapy showed that this prophylaxis was often used in a less-than-ideal manner. Patients who regularly receive warfarin should have their dosage adjusted based on their international normalized ratio (INR), a measure of clotting time. Ideally, INRs should be measured about every 28 days in patients who regularly take warfarin.

The rate of protection from stroke remained unexpectedly low among African Americans.

DR. GAGE

Among all white patients, the average time between INR measurements was 26 days; among African Americans it was 30 days. But 25% of the white patients on warfarin had an interval of 39 days or longer between INR measurements. Among African Americans on warfarin, 25% had an interval of 57 days or longer between measurements, Dr. Gage said at the conference sponsored by the American Stroke Association. For these subgroups, the interval between INR measurements was "way too long," he said.

But substandard INR monitoring was not the only reason patients got less benefit from warfarin prophylaxis, compared with the benchmark of clinical trials. The rate of protection from stroke remained unexpectedly low among African Americans even in an analysis that controlled for the frequency of INR monitoring as well as clinical variables that predispose patients to strokes.

Other factors that were not controlled for in this analysis, and that may help explain warfarin's underachievement, include poor compliance with the warfarin regimen, inadequacies in the health care setting, and inadequate access to anticoagulant services.

The trials that assessed warfarin's efficacy in patients with atrial fibrillation were highly selective; more than 90% of patients who were initially assessed for these trials were eventually excluded. The clinical trial results therefore came from patients that were mostly white, less than age 75 years, and followed very closely, and these results may not be generalizable to other health care settings, he said. ■

Restless Legs Underdiagnosed

The diagnosis of restless legs syndrome is made correctly in only 6% of symptomatic patients, Richard P. Allen, Ph.D., of Johns Hopkins University, Baltimore, and colleagues have reported.

Dr. Allen and his associates surveyed 15,391 adults in the United States and Western Europe; 1,114 (7.2%) reported all four diagnostic symptoms of RLS. Of those, about 37% (416) met the criteria for RLS sufferers (experiencing moderately or severely distressing symptoms at least twice weekly).

Most of the RLS sufferers (88%) reported sensory disturbance 60% reported pain; 76% reported sleep disturbance; 56%, impaired daytime functioning; 37%, symptoms affecting movement; and 26%, mood disturbance (Arch. Int. Med. 2005;165:1286-92).

More than 80% had discussed their symptoms with a primary care physician, but only 6% received a diagnosis of restless legs syndrome. Other diagnoses were poor circulation (18%); arthritis (14%); back or spinal problem (13%); varicose veins (7.5%); depression or anxiety (6%); and trapped nerves (6%), the investigators said.

The correct diagnosis of RLS means patients can be offered dopamine agonist therapy.

—Michele G. Sullivan

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