Capitol Sleep Medicine Newsletter

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Dreaming though Depression – Part 3

Recent Developments in Pharmacotherapy

Insomnia is a frequent symptom of depression. Although never approved by the FDA for the treatment of insomnia, the older antidepressant medication trazodone is one of the most widely prescribed medications for the treatment of insomnia. Trazodone can improve sleep continuity but common side effects are next day cognitive impairment, dry mouth, blurred vision, constipation, and urinary retention. Prolongation of the QT interval on an EKG and a lowering of the seizure threshold are other concerns. Medications in this class tend to have strong effects on sleep maintenance, but are also prone to elicit complaints of daytime sedation.[1]

A complicating factor in the treatment of depression is that antidepressant medications such as fluoxetine and other serotonin selective reuptake inhibitors (SSRIs) may disrupt sleep and worsen insomnia. Sleep improvement early in the treatment of depression should be a clinical goal.[2] Ideally, an effective antidepressant would result in normalization of disturbed sleep in concert with resolution of the depressive symptoms. Recent research studies in this field have looked at combining SSRI medications with non-benzodiazepine hypnotic medications such as zolpidem and eszopiclone.

The first two studies looked at safety in combining these classes of medications. One study looked at this using a combination of zolpidem and fluoxetine. Twenty-nine healthy female volunteers received both zolpidem (10 mg) and fluoxetine (20 mg). Both zolpidem and fluoxetine were well tolerated alone or during coadministration. The authors concluded that there were no significant pharmacokinetic or pharmacodynamic interactions between the medications and that short-term cotherapy with fluoxetine and zolpidem appears safe.[3] The second study looked at this using a combination of zolpidem and sertraline. A study looking at this in 28 healthy female volunteers determined that when compared to zolpidem alone, the presence of sertraline can slightly increase the serum concentration of zolpidem. Despite this, there were no next-day effects of zolpidem on the Digit Symbol Substitution Test, and both drugs were well tolerated. The authors concluded that coadministration of sertraline 50 mg and zolpidem 10 mg appears to be safe in healthy females but could result in a shortened onset of action and increased effect of zolpidem.[4]

Safety is one thing but do patients who are treated with such a combination improve clinically? A study of 40 men and 150 women with a combined diagnosis of DSM-IV major depressive disorder and persistent insomnia in the presence of effective and stable treatment with fluoxetine (< or =40 mg/day), sertraline (< or = 100 mg/day), or paroxetine (< or =40 mg/day) participated in a randomized, double-blind, parallel-group study. Patients received either placebo or zolpidem, 10 mg nightly, for 4 weeks and single-blind placebo for 1 week thereafter. Compared with placebo, zolpidem was associated with improved sleep as measured by longer sleep times, greater sleep quality, and reduced number of awakenings. Patients also reported feeling significantly more refreshed, less sleepy, and more able to concentrate. After placebo substitution, there was no evidence of dependence or withdrawal from zolpidem (DSM-IV criteria). The authors concluded that in this defined patient population, zolpidem, 10 mg, was effectively and safely co-administered with an SSRI, resulting in improved self-rated sleep, daytime functioning, and well-being.[5]

A larger 8 week study of 545 patients who met DSM-IV criteria for both depression and insomnia compared the effect of treating patients with a combination of eszopiclone and fluoxetine compared to treating them with fluoxetine alone. Primary endpoints were the Hamilton Rating Scale for Depression (HAM-D-17) and the Clinical Global Impression Improvement (CGI-I) and Severity items (CGI-S). Patients treated with both eszopiclone and fluoxetine had significantly decreased sleep latency, wake time after sleep onset, increased total sleep time, sleep quality, and depth of sleep at all double-blind time points. Eszopiclone co-therapy also resulted in: significantly greater changes in HAM-D-17 scores at Week 4 ($p = .01$) with progressive improvement at Week 8 ($p = .002$); significantly improved CGI-I and CGI-S scores at all time points beyond Week 1 ($p < .05$); and significantly more responders (59% vs. 48%; $p = .009$) and remitters (42% vs. 33%; $p = .03$) at Week 8. Treatment was well tolerated, with similar adverse event and dropout rates. The authors concluded that co-therapy with eszopiclone and fluoxetine was relatively well tolerated and associated with rapid, substantial, and sustained sleep improvement, a faster onset of antidepressant response on the basis of CGI, and a greater magnitude of the antidepressant effect.[6]

It may be time to rethink how we treat patients who have a combined diagnosis of depression and insomnia. This newsletter was not funded by any pharmaceutical company. Sweet dreams…

[1] Dialogues Clin Neurosci. 2006;8(2):217-26
[2] Drugs. 2005;65(7):927-47
[3] Drug Metab Dispos. 1998 Jul;26(7):617-22
[4] J Clin Pharmacol. 1999 Feb;39(2):184-91
[5] J Clin Psychiatry. 1999 Oct;60(10):668-76
[6] Biol Psychiatry. 2006 Jun 1;59(11):1052-60. Epub 2006 Apr 3