Tips from Other Journals

Tips from Other Journals are written by the medical editors of *American Family Physician.*

The trade names of drugs listed in Tips from Other Journals are based on what is currently available and not necessarily the brand of drug that was used in the study being discussed.

Effectiveness of Rifaximin for Symptomatic Relief of Irritable Bowel Syndrome

Background: Irritable bowel syndrome (IBS) is a gastrointestinal disorder that is characterized by bloating, abdominal pain, and changes in stool frequency and/or consistency. For many patients, IBS-related symptoms are not alleviated by the current treatments available. Some evidence suggests that changes in the bowel microbiota of patients with IBS may play a role in the pathophysiology. Systemic antibiotics have shown inconsistent results for symptomatic relief in patients with IBS, but a nonsystemic antibiotic, such as rifaximin (Xifaxan), could allow a targeted therapy for reduction or alleviation of IBS symptoms. Pimentel and colleagues investigated rifaximin as an effective treatment for the alleviation of bloating, abdominal pain, and loose stools in patients who had IBS without constipation.

The Study: The authors evaluated two randomized placebo-controlled trials (TARGET 1 and TARGET 2) of patients who had IBS without constipation. Patients were randomized to receive 550 mg of rifaximin or placebo three times per day for two weeks. Symptoms were recorded for an additional 10 weeks after treatment ended. Study end points were the percentage of patients with adequate relief (for at least two of the first four weeks after treatment) of global IBS symptoms, bloating, abdominal pain, and loose stools. Patients were asked to rate the average daily amounts of abdominal pain and bloating, and the average daily stool consistency.

Results: In both trials, significantly more patients in the rifaximin group (40.7 versus 31.7 percent in the placebo group) experienced adequate relief of global IBS symptoms during the first month after treatment. Significantly more patients treated with rifaximin self-reported adequate relief of bloating in both trials (40.2 versus 30.3 percent for placebo). In addition, patients receiving rifaximin self-reported significant improvement in abdominal pain and stool consistency compared with placebo. There were no significant differences in the rates of infections or other adverse events between groups.

Conclusion: Patients who have IBS without constipation experience significant relief of global IBS symptoms, abdominal pain, bloating, and loose stools after two weeks of treatment with 550 mg of oral rifaximin, three times per day.

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Source: Pimentel M, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med.* January 6, 2011;364(1):22-32.

EDITOR'S NOTE: Few pharmacologic treatments have proved effective in providing symptomatic relief of IBS. The relative ineffectiveness of most treatments could be attributed to an etiology that is most likely heterogenous.[1] Some studies suggest that alterations in the normal gut flora could be a significant contributor to the pathogenesis of IBS.[2] Earlier studies have shown inconsistent results with poorly absorbed antibiotics for symptom alleviation in patients with IBS.[3] In this study, Pimentel and colleagues provided encouraging evidence for rifaximin use in patients with IBS.

An accompanying editorial notes that although the percentage of patients reporting symptom alleviation compared with placebo (9 to 12 percent more with rifaximin) is statistically significant, it is of modest clinical relevance.[4] Additional areas of concern are the chronic nature of IBS and bacterial resistance. Pimentel and colleagues studied a one-time treatment and its effectiveness during a short-term period (10 weeks after the initial two-week treatment phase); it is unclear if symptomatic relief would persist or if retreatment would be equally efficient if required. IBS is a relatively common condition, and widespread rifaximin use has the potential to alter bacterial resistance profiles in the intestinal tract over time. Currently, rifaximin is not approved by the U. S. Food and Drug Administration for

the treatment of patients with IBS. More studies evaluating rifaximin as a long-term or intermittent IBS therapy would be useful in assessing the drug's potential as a reliable IBS treatment. Nonetheless, the TARGET 1 and TARGET 2 short-term trials have provided optimism for rifaximin as an effective IBS treatment, and it should be added to the list of other IBS therapies currently available.—B.M. and SUMI SEXTON, MD, Associate Editor, *American Family Physician*

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Improving Insomnia with Melatonin, Magnesium, and Zinc

Background: Insomnia affects up to 50 percent of older adults, and has been correlated with morbidity and mortality in this population, as well as poorer quality of life. Melatonin supplementation may improve total sleep time because of its effect on regulating the sleep-wake cycle. This may be particularly useful in older patients, because of an age-related decline in melatonin production and because melatonin levels are lower in adults with insomnia than in those who report getting good sleep. Other micronutrients such as zinc and magnesium may also play a role in facilitating sleep because they are important in the endogenous synthesis of melatonin. Rondanelli and colleagues conducted a double-blind, placebo-controlled clinical trial to determine whether melatonin, magnesium, and zinc would improve symptoms of insomnia among older adults living in a long-term care facility.

The Study: The authors recruited 43 adults 70 years and older living in a long-term care facility who had been diagnosed with primary insomnia, defined as difficulty in initiating or maintaining sleep for at least one month with no sign of any other contributing sleep or mental disorder, drug use, or other general medical condition. Exclusion criteria included anxiety, depression, psychosis, or the use of beta blockers or other medications that affect the central nervous system, such as benzodiazepines and other sleep-inducing agents.

Patients were randomized to treatment with placebo or a combination of melatonin (5 mg), magnesium (225 mg), and zinc (11.25 mg) administered one hour before bedtime daily for eight weeks. The primary outcome was sleep quality as defined by the Pittsburgh Sleep Quality Index (PSQI), which was measured at baseline and again at the end of the study. Secondary outcomes were changes in sleep quality and daily activity according to other questionnaires, including the Leeds Sleep Evaluation Questionnaire (LSEQ).

Results: The treatment group reported more significantly improved sleep quality (mean PSQI improvement of –7.1 points from baseline versus –0.3 points for the placebo group; $P < .001$). Significantly more patients in the treatment group had a final PSQI score of 5 or less, a cutoff that is 89.6 percent sensitive and 86.5 percent specific in differentiating good sleepers from poor sleepers (59 percent in the treatment group versus 14 percent in the placebo group; $P = .004$). The treatment group also had significantly better scores in all four components of the LSEQ, including getting to sleep, sleep quality, hangover on awakening from sleep, and alertness the following morning. No differences were noted in daytime sleepiness between groups.

Conclusion: Sleep quality was significantly improved among older adults living in a long-term care facility who received a nightly dose of melatonin, magnesium, and zinc, as was morning alertness. The authors suggest that this may also be a helpful sleep aid for the general older population.

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Source: Rondanelli M, et al. The effect of melatonin, magnesium, and zinc on primary insomnia in long-term care facility residents in Italy: a double-blind, placebo-controlled clinical trial. *J Am Geriatr Soc.* January 2011;59(1):82-90.

Escitalopram Effective for Reducing Hot Flashes in Menopausal Women

Background: Menopausal hot flashes can be treated effectively with estrogen and progesterone, but concerns about the risks of hormonal treatment have greatly curtailed their use. Currently, there are no other treatments for hot flashes approved by the U.S. Food and Drug Administration, and studies of other agents, including selective serotonin and serotonin-norepinephrine reuptake inhibitors, have shown varied results. Freeman and colleagues studied the effectiveness of escitalopram (Lexapro) on the frequency, severity, and bother of hot flashes in menopausal women.

The Study: This multicenter, randomized, placebo-controlled study recruited healthy perimenopausal or postmenopausal women between 40 and 62 years of age.

Women who reported frequent hot flashes (at least 28 hot flashes or night sweats per week that did not decrease significantly between weeks 1 and 3) that were rated as bothersome or severe at least four days a week were eligible to participate. Exclusion criteria included current or recent use (within the past 30 days) of psychotropic medication or any other prescription, over-the-counter, or herbal remedy for hot flashes; use of hormonal therapies or contraception, selective estrogen receptor modulators, or aromatase inhibitors in the past two months; and severe medical or mental illness. Menopausal and general health status were assessed before randomization at two clinic visits with a history and symptom diary review, physical examination, and laboratory testing.

Participants were randomized to receive 10 mg of escitalopram or placebo for eight weeks. If the frequency of hot flashes did not decrease by at least 50 percent or the severity did not decrease after four weeks, the dosage was increased to two tablets per day. Participants continued recording hot flash frequency, severity, and bother during the course of the trial. Women taking two tablets per day at the end of eight weeks tapered the dose over a week, and persons taking one tablet stopped at eight weeks. Adherence and adverse effects were assessed through a telephone interview one week after randomization and at clinic visits at weeks 4 and 8. A final telephone interview was conducted at week 11 to assess return of symptoms, adverse events, or withdrawal symptoms.

Results: The primary outcomes were hot flash frequency and severity (expressed as the seven-day mean) at weeks 4 and 8. Frequency was calculated as the number of hot flashes or night sweats over 24 hours. Severity was rated as mild, moderate, or severe. Secondary outcomes included hot flash bother (none, a little, moderately, a lot) and clinical improvement from baseline (a decrease in hot flash frequency of at least 50 percent). A decrease in hot flash frequency of at least 75 percent was also evaluated. Linear regression modeling accounted for any differences among race, and any effect of baseline depressed mood or anxiety.

A total of 104 women were randomized to receive escitalopram and 101 were randomized to receive placebo. In both groups, the baseline hot flash frequency was 9.78 per day. By the fourth week, 51 percent of the escitalopram group and 70 percent of the placebo group increased their dosage to two tablets per day because of the lack of symptom improvement. By week 8, women in the escitalopram group had a significant decrease in hot flash frequency compared with placebo (4.60 fewer per day compared with 3.20 fewer), and hot flash severity and bother were significantly decreased in the escitalopram group compared with placebo. A decrease in hot flash frequency of at least 50 percent from baseline was achieved in 55 percent of the treatment group versus 36 percent of the placebo group. Similarly, a decrease of at least 75 percent from baseline was achieved in 19 percent of the treatment group versus 9 percent of the placebo group. Race, depressed mood, or anxiety did not significantly modify the treatment effect. Adverse effects in both groups were similar. At the 11-week follow-up, women in both groups reported increasing frequency of hot flashes, but the increase was higher in the escitalopram group than in the placebo group. Severity and bother ratings also increased in the escitalopram group but not in the placebo group at week 11. When asked if they would like to continue their assigned medication, 64 percent of women in the escitalopram group said they would, compared with 42 percent in the placebo group.

Conclusion: Although the placebo effect is expected in hot flash studies and was moderate in this study, escitalopram at a dosage of 10 or 20 mg per day effectively reduces hot flash frequency, severity, and bother compared with placebo.

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Source: Freeman EW, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA*. January 19, 2011;305(3):267-274. ■