A little better than placebo is still better than nothing

Adrian S Dobs

Doctors often dismiss drugs as ineffective if they fail to outperform dummy pills in randomized trials. That's a mistake. When active medicines have few side effects and produce a strong placebo effect, such drugs, even if they prove just slightly better than placebo, should be embraced for the relief they can bring to patients who have few safe alternatives.

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The US Food and Drug Administration (FDA) usually follows the advice of its advisory panels of outside experts, but not always. Fortunately, on 28 June the agency made the rare decision to ignore the recommendations of an advisory panel of which I was a member. That day, the FDA approved the use of low-dose paroxetine for the treatment of vasomotor symptoms—hot flashes and night sweats—in post-menopausal women.

Several months earlier, the majority of the FDA's Advisory Committee for Reproductive Health Drugs had actually voted 10-4 against paroxetine's approval. They cited clinical trial data showing that the drug provided little additional benefit compared to placebo. I was also a member of the committee, but I was in the minority. "I have no problem with the placebo effect," I told my fellow panelists as I explained my 'yes' vote at the March 2013 meeting. In fact, I believe doctors need to embrace the placebo effect and use it to our advantage whenever ethically feasible. To say that there's a strong placebo component to a drug's effect should be taken as a given—and it's not necessarily a bad thing.

Treatment options are sparse for the debilitating signs and symptoms of the transition into menopause. Systemic estrogen therapy, either alone or combined with progestin, has been shown to significantly reduce the frequency and severity of hot flashes. Yet, concerns about the risks of breast cancer and blood clot formation have resulted in a dramatic decline in estrogen use in recent years. Nonhormonal attempts at treatment have been disappointing. Studies using soy, black cohosh (an herbal remedy) or other phytoestrogens have been essentially negative, leaving 'toughing it through'—often by layering clothing during the day and alternating between thin sheets and thick blankets at night—as the only remaining choice for many women.

Paroxetine provides a much-needed nonhormonal alternative. The selective serotonin reuptake inhibitor that has been used for decades to treat depression, most commonly under the brand name Paxil. Similar to other studies in which astute researchers noted a secondary benefit during a drug trial—think Rogaine or Viagra—clinicians testing the antidepressant effects of paroxetine noted that postmenopausal women experienced fewer hot flashes¹. Investigators then did a dose finding study to discern that 7.5-milligram pills were effective for postmenopausal hot flashes and averted some of the debilitating side effects, including weight gain and sexual dysfunction, that women experience when taking higher doses of the drug. (The lowest available dose of paroxetine for treating depression is 10 milligrams per pill; most people take 20- or 40-milligram doses.)

In two pivotal studies involving a total of 1,174 postmenopausal women, participants who took 7.5-milligram pills of paroxetine daily and had a median baseline hot flash frequency of approximately ten per day saw their hot flash count cut to around six per day after four weeks and down to four or five after 12 weeks. By comparison, women receiving placebo pills had an average of around seven and six hot flash episodes after four and 12 weeks, respectively. The difference between the two groups, although statistically significant, was clearly marginal. But the benefit provided by either treatment compared to baseline was huge.

This outcome should not surprise anyone. Placebos work. They are effective against pain, depression and even healing after minimally invasive surgery. Since the publication of Henry K. Beecher's *The Powerful Placebo*² more than half a century ago, doctors have appreciated that placebos have medically important effects. And in clinical trials, responses to placebos are often especially pronounced because participants typically respond favorably to any intervention simply because of their awareness of being under observation—a phenomenon known as the 'Hawthorne effect'.

Many have argued that a placebo should be part of the medical armamentarium. However, the standard of care in the US, for good or bad, is to exclude the prescription of dummy pills. Their use is perceived as deceitful and thought to violate the essential principle of informed consent. So, without the ability to offer placebo pills to my patients, I for one will gladly write prescriptions for paroxetine to combat hot flashes—and not off-label prescriptions at doses that carry a high risk of side effects, as many women now receive the drug, but prescriptions at the low dose recently sanctioned by the FDA for this indication.

It's true that the 7.5-milligram capsules of paroxetine—which will be marketed by Noven, a US subsidiary of the Japanese pharmaceutical company Hisamitsu, under the brand name Brisdelle, starting in November—will undoubtedly be more expensive than generic versions of Paxil. But taking a standard dose with a proven clinical record is safer and more convenient than pill splitting. Plus, the approved version of paroxetine (paroxetine mesylate) for hot flashes has a different chemical structure than the widely available generic (paroxetine hydrochloride), and there are some suggestions that people metabolize these two formulations in unique ways³.

According to data presented at the March meeting of the Advisory Committee for Reproductive Health Drugs, pharmacies in the US fill more than 3 million prescriptions per year for antidepressants for the off-label treatment of vasomotor symptoms. Putting aside the lack of prescribing information and the potential for side effects, that number is still a drop in the bucket compared to the total number of postmenopausal women who could benefit from such a nonhormonal therapy. The approval of low-dose paroxetine will raise awareness of this drug option and help address an unmet medical need in a safe and effective manner. If the benefit is largely driven by a placebo effect, so be it—it's still a benefit nonetheless. Women should not be deprived of this option.

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