Imagine, as a psychiatrist, hearing this story from a beloved friend or relative:

“I’ve been terribly depressed for the last month—can’t focus, can’t get out of bed, and I’m barely eating. Nothing really gives me pleasure anymore. I haven’t showered in 2 weeks. Sometimes I think I’d be better off dead. I asked my family doctor if an antidepressant might help. She said I’d do just as well taking a sugar pill, and it’s a lot cheaper!”

I hope you would be both alarmed and outraged by this doctor’s dismissive attitude. Yet if the doctor—or your loved one—had read the article on antidepressants in the February 8 Newsweek (The Depressing News About Antidepressants), she might well have concluded that antidepressants are largely worthless.

Let’s credit Newsweek and the usually careful science writer, Sharon Begley, with bringing the problem of clinical depression before a wide audience. The clever cover of the magazine allows one to read either “Antidepressants Don’t Work” or “Antidepressants Do Work,” depending on which title is on top. Sadly, the article itself is a bit topsy-turvy, and may do less to educate the general public than to confuse or alarm it. (A nice rebuttal by psychiatrist Robert Klitzman, MD follows the Begley article).

Essentially, after a superficial analysis of 2 recent studies, Begley concludes that antidepressants are “basically expensive Tic Tacs” (sugar pills). Begley then struggles with whether it might be “a kindness” to keep patients “in the dark about the ineffectiveness of antidepressants, which for many are their only hope…”

The studies in question—by Kirsch and colleagues and Fournier and colleagues—found that antidepressants were not substantially more effective than placebo, except for the most severe types of depression. The lay press promptly proclaimed—sometimes with barely suppressed glee—“Antidepressants No Better than Sugar Pill!”

Both the Kirsch and Fournier studies are “meta-analyses” of various individual antidepressant trials. Meta-analyses suffer from all the problems common to such “number-crunching” methods: if the individual studies are flawed, the meta-analysis is flawed. For example, the Kirsch meta-analysis looked only at studies carried out before 1999. The much-publicized Fournier study examined a total of 6 antidepressant trials (n=718) using just 2 antidepressants, paroxetine and imipramine. Two of the imipramine studies used doses that were either subtherapeutic (100 mg/day) or less than optimal (100 to 200 mg/day). Moreover, the design of the Fournier study intentionally excluded individual studies.
involving a “placebo washout” phase, which attempts to reduce the number of placebo-responders receiving active medication. By excluding such studies, the Fournier meta-analysis may have reduced the difference between placebo and antidepressant response rates.

The Newsweek article also misrepresented the nature of placebo controls. Begley repeatedly describes a placebo as a “dummy pill”—but subjects in the placebo group of most major antidepressant studies receive much more than a sugar pill. As research psychiatrist Dr. Sheldon Preskorn recently wrote me, “…there is much more treatment [provided] by being on a placebo in a study than most depressed patients get in routine clinical practice, particularly in the primary care setting” (personal communication, 2/03/10). Indeed, Preskorn estimates that in a typical 8-week trial, a subject in the placebo group may receive 10 to 12 hours of contact time with knowledgeable and empathic healthcare practitioners. In effect, the placebo control is a kind of substantive, supportive intervention. Furthermore, placebo group response rates in depression studies have been mysteriously and substantially rising in recent decades—perhaps in part because less severely depressed subjects are being recruited. Since mildly depressed subjects are more likely to be placebo responders, such a recruitment artifact could be shrinking the difference between antidepressant and placebo response rates.

Moreover, the Newsweek article—like many professional journals—also ignores an important underlying reason for the diminishing drug-placebo difference, as we move from more severe to milder forms of depression. As Preskorn explains, “The ‘finding’ that antidepressants do not work as well in mild as in severe depression is a ‘floor’ effect. [One] could not show that antidepressants worked in non-depressed individuals, and the lower the severity score, the closer the participants are to the ‘floor’” (personal communication, 1/19/10).

Begley acknowledges the benefit of antidepressants in severely depressed patients, but minimizes its importance, noting that only 13% of patients meet this severity threshold. But based on a 2004 SAMHSA study, “only” 13% means that about 2 million adults in the United States may suffer from severe depression in a given year. Even by the lights of the Fournier study, that’s 2 million people who would probably respond well, acutely, to an antidepressant. Furthermore, as Preskorn notes, acute efficacy studies, in contrast to maintenance studies, “…overestimate the efficacy of ‘placebo’ treatment. On average, 3 out of 10 fewer patients will relapse in 1 year if they are continued on medication, as opposed to being switched to placebo.”

Yes, antidepressants are “oversold” in those Big Pharma ads, adorned with chirping birds and fluttering butterflies—in truth, antidepressants don’t work as well or as specifically as we’d like. Given the frequent side effects of many antidepressants, it is usually wise to initiate treatment with psychotherapy, in cases of mild-to-moderate, non-melancholic depression. Alas, psychotherapy is often difficult for patients to obtain or afford. Despite Newsweek’s supposedly “depressing news” about antidepressants, psychiatrists have good reason to keep these medications in their armamentarium—and patients with severe unipolar depression have good reason to consider taking them.

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References