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## ARTICLE

### *Antidepressants: Progress or Promotion?*

Richard J. DeGrandpre

Some leading drug companies are promising that a new generation of antidepressants is on the way. That would be welcome, comments the author, because today's medications fail to help a significant percentage of patients, especially the most seriously depressed. But the problem is that one of the widely anticipated new drugs appears to revert to the same principles of action that characterized the antidepressants of an earlier era. What is going on here?



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by Richard J. DeGrandpre, Ph.D.

## Antidepressants: Progress or Promotion?

*Half-a-century ago, the first antidepressant effects were discovered by sharp-eyed scientists testing drugs intended for entirely different purposes. The soaring popularity of today's antidepressants rests, in part, on the belief that, in the years since, we have come to understand the causes of depression in terms of chemical imbalances in the brain and how new generations of antidepressant drugs address them. Unfortunately, argues the author, that belief may be more a product of success in marketing than in research. He lays out the troubling contradictions in successive explanations of depression and the actual effects of the drugs used to treat it. To help millions of the still seriously ill, he argues, research and innovation, not imaginative marketing campaigns, should be our priority.*

In its 2003 report *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, the president's Council on Bioethics concludes that, "We want to perform better in the activities of life—but not by becoming mere creatures of our chemists or by turning ourselves into tools designed to win and achieve in inhuman ways." The report continues: "We want longer lives—but not at the cost of living carelessly or shallowly with diminished aspiration for living well, and not by becoming people so obsessed

with our own longevity that we care little about the next generations. We want to be happy—but not because of a drug that gives us happy feelings without the real loves, attachments, and achievements that are essential for true human flourishing."

These are important sentiments, especially at a time when happiness seems to be in danger of being turned into simply a problem of chemical balances. Having said this, however, it is important to remember that there are those who will not find happiness of any lasting kind without some type of intervention, chemical or otherwise. According to a 1999 Surgeon General's report, still among the most comprehensive on mental health, up to seven percent of people in the United States suffer from mood disorders, including depression, each year. Women between the ages of 18 and 45 comprise the majority of those with depression, it being diagnosed twice as often in women as in men. According to a 2002 report by the American Psychological Association, puberty, pregnancy, trauma, substance abuse, and the quality of one's relationships are all linked to an increase in risk of depression in women, with no economic or racial group left untouched.

Mood disorders involve a range of psychological difficulties, including anxiety,

depression, mania, and bipolar disorder. These problems can be distinguished from normal fluctuations in mood—in part by their association with higher rates of other illnesses and death. Also, depression of the clinical kind is qualitatively different from the blues, malaise, or sadness. For example, depression can involve considerable anxiety, and sufferers often feel a degree of pain and despair that, when coupled with a looming sense of hopelessness, can lead to suicide or suicide attempts.

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The prevalence of depression (and other mental disorders, including schizophrenia) is increasing. Epidemiologist Myrna Weissman, Ph.D., and her colleagues explored this phenomenon in two reports that appeared in 1992 and 1996 in the *Journal of the American Medical Association*. They concluded that, first, more Americans are becoming depressed, second, that they are getting depressed at a younger age, and, finally, that the severity and frequency of depression are rising. Even after changes in definition and diagnosis are taken into

account, the data show that each generation born in the 20th century experienced more depression than previous generations, with the overall rate of mood disorders more than doubling since World War II.

For the many people who suffer clinical depression, the real question is not: Is it acceptable to achieve happiness through chemistry? It is whether the use of drugs to treat depression has anything like the rate of success that the president's Council worries may produce a culture of happiness-in-a-pill. The Council is certainly right that this sure fix is the public impression fostered by a decade or more of intensive marketing of drugs for depression. Unfortunately, however, there are disturbing signs that that promotion may have raced far ahead of the progress made in either understanding or treatment.

#### **A CURIOUSLY CIRCULAR PATH OF PROGRESS**

Consider a recent, intriguing chapter in the saga of Eli Lilly and Company's antidepressant Prozac. Only one among several of the SSRIs (selective serotonin reuptake inhibitors), Prozac is often singled out, not because it is unique, but because it is perhaps the most commercially successful pharmaceutical product of our time, having become virtually synonymous with the marketing campaigns that thrust antidepressants into the mainstream of American life.

With the patent fairly recently expired on Prozac, Lilly has since announced that it hopes to bring a new antidepressant to market during 2004. This drug, duloxetine, would be sold under the trade name Cymbalta.

According to Lilly's Web page, the drug represents an advance on Prozac in that it "enhances levels of two important brain chemicals." This claim by Lilly is, to say the least, remarkable, because this dual-action agent affects both serotonin and norepinephrine.

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To understand why this recent embrace of a dual-action compound by a leading antidepressant manufacturer is so surprising, we need to look back a decade or more to when Prozac began making headlines. The first medications specifically developed for depression were what are called tricyclic antidepressants, because the chemical compounds were three-ringed. The tricyclics all prevented ("blocked") nerve cells from inactivating the neurotransmitters, or chemical messengers, serotonin and norepinephrine. Then, in the 1990s, Lilly succeeded beyond expectation in suggesting that a new, revolutionary class of drugs had come into being, with Lilly's Prozac as the leader. These new drugs, the SSRIs, specifically target serotonin, low levels of which were said to be the cause of depression. A two-page advertisement in popular magazines in 1997 and 1998 proclaimed that "Depression is a real illness with real

causes. It can be triggered by stressful life events...To help bring serotonin levels closer to normal, the medicine doctors now prescribe most often is Prozac."

Part of the success in making Prozac a household name, and linking the drug with the idea of a chemical imbalance, came from psychiatrist Peter Kramer's popular best-seller *Listening to Prozac* (Viking, 1993). Consistent with Lilly's claims, Kramer told readers that Prozac represented an advance because it targeted serotonin while bypassing norepinephrine, the latter being the neurotransmitter blamed by Lilly for many of the side effects of earlier antidepressants. Thus, we read in *Listening to Prozac* that the "mainstay" of tricyclic antidepressants (imipramine), "is 'dirty' in its main effects and its side effects because it affects both norepinephrine and serotonin. Once imipramine's mechanism of action was understood, pharmacologists set out to synthesize a 'clean' antidepressant." This "clean" antidepressant, of course, was Prozac.

On the heels of Kramer's book, stories in popular weekly magazines followed. For instance, a *Time* article in 1997, "The Mood Molecule," described the tricyclic medications, saying that "In the 1960s, a [new] class of antidepressants emerged...[They] had major side effects, though, including profound drowsiness and heart palpitations. The reason, scientists generally agreed, was that they affected brain chemistry too broadly. The research seemed to point to serotonin as the most important mood-enhancing chemical...so neurochemists set about looking for a drug that would boost the influence of serotonin alone."

Now, however, we are told that Lilly has engineered a dual-action drug that is better than Prozac, because Prozac's efficacy was based on targeting only serotonin, not norepinephrine. If the claims were true about why the SSRIs were better than the tricyclics, it is difficult to understand how dual-action Cymbalta could represent a breakthrough, because it acts on the brain in much the same manner as did most earlier, tricyclic antidepressants. If, on the other hand, the new claims about Cymbalta are true, the story behind the SSRIs seems to make no sense, because affecting norepinephrine is now said to be a good thing.

Few if any media reports have taken notice of this contradiction, despite the many provocative questions raised by Lilly's return to dual-action agents. Among these questions is whether, or to what extent, the American public—or even physicians—can distinguish between the science of drug development, on the one hand, and the science claims of drug marketing, on the other. Going back to dual-action antidepressants also raises the question of what we really know today about the physiology of depression and how brain-altering drugs (and other treatments) influence it. Do we have a good understanding of depression and the actions of antidepressants, even if drug companies sometimes are led to shade this understanding when their “new” product does not quite fit with it? Or, rather, might it be the case that medical and pharmaceutical science remains in the dark, leaving the drug industry to make up stories to sell their wares in what remains a huge and competitive marketplace?

## MOODS AND BRAIN CHEMISTRY

The basic idea that there might be a link between our moods and our brain biochemistry evolved out of serendipitous discoveries. Beginning in the 1950s, drugs used to treat symptoms of various physical illnesses such as allergies and hypertension precipitated unsolicited and surprising reports of improved mood in patients. Dubbed “psychic energizers” rather than “antidepressants,” these medications were sometimes described as “lifting” mood and, at other times, as causing patients to feel “better than well.”<sup>1</sup>

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Today, we take for granted that a connection exists between drugs and brain biochemistry, and indeed compounds currently classified as antidepressants (including the SSRIs) do have measurable effects on biochemical systems. But the causal relationship between such specific, direct effects on brain chemistry and broader clinical effects on mood remains murky. A chief problem is uncertainty about which of the physiologic effects (primary, secondary, or still-more-distant) produced by a particular drug are actually responsible for the changes in mood.

Prozac: Panacea or Pandora?  
**From the Era of the Asylum to the Age of Prozac**  
*Nature's Prozac*  
**Listening to Prozac**  
**Beyond Prozac**  
*Plato, Not Prozac!*  
**Prozac: The Controversial Cure** *Let Them Eat Prozac*  
**PROZAC NATION**  
*Prozac-Free* **THE NATURAL PROZAC PROGRAM**  
**7 Reasons Kids Have Fun While Adults Have Prozac**  
**Better Living from Plato to Prozac** **Prozac As a Way of Life**  
*Prozac Highway*  
**Prozac Backlash**  
**BETTER THAN PROZAC** **Talking Back To Prozac**  
*Natural Prozac* *Potatoes Not Prozac*  
**Prozac on the Couch**

In the 1990s, a new generation of drugs such as Prozac was hailed in a flood of books, magazine articles, and advertisements as providing an innovative treatment for the chemical imbalances said to cause depression. By virtue of its market success, Prozac came to represent in the public's mind the pros and cons of all the anti-depressants, as this sampling of book titles shows.

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Further study of the neurobiological causes and correlates of depression, and how antidepressants affect them, thus remains critical. In the search for answers, one approach has been to work backward from discoveries of a link between a drug's action and improvement or worsening of mood. Observation of the effects of an effective tricyclic compound known as clomipramine is a case in point. Compared to other tricyclics, it affects serotonin more than norepinephrine, and this led some researchers in the 1960s to ask whether compounds

that acted even more "selectively" on serotonin might be even more effective in treating severe depression. This was the observation that eventually led to the development and patenting of "selective" serotonin reuptake inhibitors in the early 1970s.

In contrast, other research has taken a direct neurobiological approach, probing for neurologic or biochemical differences in patients diagnosed as clinically depressed. For example, research of this type demonstrated abnormal concentrations of various neurochemicals and their metabolites in

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urine, plasma, and cerebrospinal fluid across different subgroups of depressed individuals. The exact meaning of these differences for depression and its treatment has not, however, been easy to determine.

### THE MONOAMINE HYPOTHESIS

Among the first formal explanations tendered for the specific biochemical basis of depression was the “monoamine hypothesis,” which asserted that individuals who suffer depressive episodes might have a deficiency of monoamine neurotransmitters in their brains. This group of neurotransmitters includes serotonin, dopamine, epinephrine, and norepinephrine. The monoamine theory arose in the 1950s, when a natural alkaloid compound called reserpine came into use as an antihypertensive drug and later as an antipsychotic. In the brain, reserpine binds to and permanently damages structures at the synapses between neurons in the noradrenergic (norepinephrine) and dopaminergic (dopamine) systems. This action causes cells to lose their capacity to maintain an effective concentration of dopamine and norepinephrine. Reserpine, therefore, is called an “antagonist” to the synaptic transmission of these neurotransmitters.

Although one of the first reports of reserpine’s effects on mood states—a study published in the *Annals of the New York Academy of Science* in 1954—found it to be an antidepressant, other studies at the time, including two in the *Lancet* in 1955, linked the compound to increased incidence of suicide and attributed this effect to a worsening of mood. Because reserpine reduces levels of norepinephrine as well as serotonin,

the *Lancet* reports encouraged the hypothesis that perhaps compounds that raised levels of these neurotransmitters function as antidepressants. A related theory, the “catecholamine hypothesis,” stressed that reserpine actually affects three members of a group of neurotransmitters called the catecholamines, namely norepinephrine, dopamine, and epinephrine.

Meanwhile, the mysterious finding that reserpine was an antidepressant for some patients got left behind. To explain this oversight, psychiatrist and historian of psychiatric medicine David Healy makes the point that, although it was true that with reserpine there were increased problems of suicide, these suicides resulted not from a depressant effect on mood but, rather, from isolated instances of agitation and restlessness (a syndrome known as akathisia). Healy noted that reserpine does indeed have antidepressant properties even though its action on the monoamines is opposite those of tricyclic antidepressants (and, to a lesser extent, the SSRIs).<sup>2</sup> It becomes obvious that the monoamine hypothesis alone cannot explain how both reserpine and a tricyclic drug—one an antagonist and the other an agonist (or promoter) of catecholamines—lessen the symptoms of depression. No doubt this seeming contradiction is one reason that, as the monoamine theory gained momentum, the positive report of reserpine’s effect on mood was dropped.

But other findings soon surfaced that raised doubts. In fact, from the beginning amine theories have coexisted alongside evidence contradicting them. As early as 1953 and 1955, for example, clinical reports

described how the tuberculosis drug isoniazid functioned as an antidepressant in a non-hospitalized population, even though it has no effect on either norepinephrine or serotonin. As demonstrated in the case of

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reserpine, moreover, some compounds that improve mood over time have actions quite the opposite of the tricyclics. Lithium, for instance, is effective in dampening depressive symptoms in individuals diagnosed as manic-depressive, even though lithium decreases rather than increases levels of norepinephrine.

The truth is that no reliable relationship has been identified between depressive states and levels of any known biochemical system, including systems involving norepinephrine and serotonin. Individuals can differ in their metabolism of amines such as norepinephrine, and these differences can influence responsiveness to certain antidepressant drugs, but this is not the same as demonstrating that many, most, or all persons who experience depression do so as a result of low amine levels. In fact, such individual differences apply to many other neurotransmitter systems. What is more, although some drugs sold as antidepressants are more efficacious than others in their actions on norepinephrine (or even serotonin),

none shows greater efficacy than the others in treating depression. This lack of relationship applies both to the tricyclics and the SSRIs.

Additional difficulties for amine theories stem from the effects of antidepressants over time. The biochemical actions of tricyclics and SSRIs occur after short-term use, but the clinical effects emerge only after longer use. In fact, studies show that by the time the clinical effects of the drug do emerge, often the neurotransmitter levels have returned to their pre-drug levels. This suggests that the clinical effects of the drugs could be due to some indirect, downstream effect, with the temporary rise in neurotransmitter levels only a step in the causal chain.

These negative findings have long raised doubts about the validity of any amine, deficiency, or imbalance hypothesis. That such hypotheses persist suggests that their virtue has to do with something other than scientific evidence. As Healy wrote in *Let Them Eat Prozac*, “The monoamine theories had tremendous slogan value but little else.”

#### **GRAPPLING WITH THE COMPLEXITY**

The caption on a 1994 *Science* magazine graphic showing Prozac’s actions on serotonin receptors reads: “Prozac blocks the serotonin transporter in the membrane of the nerve terminals. The resulting increase in the duration of action of released serotonin is, after several weeks, somehow translated into multiple therapeutic effects.” This “somehow translated” reminds us how much remains to be learned about depression and the way it is affected by antidepressants. It also reminds us that

behind the amine hypotheses there still lies an undeniable truth: Drugs deemed antidepressants do have biochemical actions and these actions do sometimes translate into clinically significant effects. The theoretical shortcoming of amine and other biochemical hypotheses is not so much their reliance on this insight, but rather their persistent oversimplification of its meaning.

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In most psychopharmacology textbooks, one encounters the pleasing notion that a drug has direct, identifiable neurochemical actions, and that these actions are responsible for the drug's psychologic effects. Prozac is a serotonin reuptake inhibitor, cocaine is a dopamine reuptake inhibitor; both increase feelings of well-being. The problem is that it is not sufficient to understand antidepressants just in terms of their action at the receptor. A case in point is a structure in the center of the brain, the raphe nuclei, that contains serotonergic neurons. When these neurons are stimulated by an SSRI, they, in turn, inhibit dopaminergic neurons in another area of the brain, known as the substantia nigra. The substantia nigra, furthermore, contains neurons that communicate with still other structures in the brain. In addition, the initial effects

of at least some SSRIs on serotonin in the raphe nuclei are different from the long-term effects. Although an initial dose of Prozac has been shown to increase serotonin production in the raphe nuclei, long-term use has been shown to have just the opposite effect.

Of course, all this unfolds not in static isolation but rather within a particular human being, a dynamic biological cosmos with a diverse environment and a unique history of development. The magnitude and meaning of the effects of antidepressants, therefore, also depend in part on individual differences that arise from both genetic (nature) and developmental (nurture) factors. An example of this complexity, which we might call the "ecology of depression," is provided by research on stress and depression.

How a person experiences stress clearly affects that person's individual health, including mental functioning, and has thus received growing attention as part of the study of anxiety and depression. In addition to discovering that there are biological and psychological risk factors affecting an individual's response to stress, researchers have identified certain groups particularly at risk. Women, the young, unmarried adults, African Americans, and people with low socioeconomic status all experience greater stress and, in turn, a higher incidence of depression. Single mothers, for example, have nearly twice the risk of depression as do mothers who are married. These and other discoveries have led some to call depression a "syndrome of stress."

What this research seems to show is that a person's risk of depression and the severity and course of that depression are

influenced by both exposure to stress and a person's coping ability. Chronic stress can cause a general and prolonged sensitization of the arousal response in the nervous system, and this hypersensitivity has been shown, in turn, to cause problems of anxiety and mood. Tracking the effect of stress is complicated. Research in this area focuses not just on the monoamines but also on the connected series of structures in the brain called the hypothalamic-pituitary-adrenal axis and how this axis is affected by corticotropin-releasing hormones, which are neuropeptides released by the hypothalamus to activate the pituitary gland. As stress impacts a person, the immune system responds by increasing the activity of the immune cells called cytokines. Chronic cytokine synthesis and release can, in turn, cause long-term changes in the brain's stress-response system, hypersensitizing the brain so that even minor stresses cumulatively affect the health of the individual.

These and related discoveries suggest a theory of depression in which at least some cases stem from external factors. And, although this is only one example of ongoing research, it makes a larger point: The world of the individual and the world of the brain come together to create an ecology of depression that is marked by complexity. We must grapple with that complexity if we are to advance in the prevention and treatment of depression.

#### **MULTIPLE PATHWAYS TO HELL—AND BACK**

“There may be nothing in the brain that corresponds to what the clinical psychiatrist describes as a major depression,” wrote

neuroscientist Steven Maier in the August 25, 2003, issue of *The Scientist*. This comment raises another basic question involving amine hypotheses, namely, whether depression has a uniform and consistent set of causes. Although a common set of symptoms lead physicians and therapists to diagnose depression, and although society talks about depression as a single entity, the evidence suggests that there are, in fact, multiple depressions—or, to be more specific, multiple pathways to depression. If so, theories of biochemical deficiencies are not only simplistic in terms of drug-receptor interactions, they are also simplistic in terms of causality.

Nor is this merely an issue of depression ranging in severity from general malaise to clinical depression. Depression varies in its causes even among those experiencing depression of equal severity. Add to this conclusion one additional point, and the implication becomes clear. If depression has myriad origins—some more biological, some more psychological, some more historical—does this not also mean that different cases of depression might, in fact, require different treatments? And if this is true, might it not also be the case that the current “one pill fits all” approach to depression leaves many who suffer it essentially untreated?

Much in the current state of treatment points in this direction. For example, antidepressants were once used only in the most severe cases of depression, at a time when it was “not fashionable to be depressed,” as Nathan Kline put it in 1964. Unfortunately, research shows that today's most widely used antidepressants, the SSRIs, are not even

effective in this population. If SSRIs represented any kind of breakthrough for some patients, they actually represented a setback for patients most afflicted by depression.

As regards the heterogeneity of depression, several recent studies are interesting. One study, published in 2002 in the *American Journal of Psychiatry*, compared the effects of a placebo with drug treatment (either Prozac or Effexor). After sorting individuals suffering from clinical depression into two comparable groups, researchers compared the physiologic changes resulting from the two treatments.

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What was interesting about the study was not just that many individuals in the placebo group improved (38 percent) but also the physiologic changes that were observed. All participants who improved, whether treated with a placebo or an antidepressant, showed measurable brain changes that correlated with their improved symptoms. However, the nature of these changes was different. Measuring the electrical activity in certain areas of the brain with an electroencephalogram (EEG) over a nine-week period showed that participants who responded to medication had reduced activity in the prefrontal

cortex, whereas those who responded to the placebo showed increased activity in this area. The discovery that different treatments might not only be effective, but be effective by way of different mechanisms of action in the brain, suggests that some treatments could indeed be more helpful for some individuals than for others.

Assuming that the duration of some of these effects may also differ, it suggests that perhaps some treatments may be more lasting than others.

A later study, conducted by other investigators and published in 2004 in *Archives of General Psychiatry*, affirms these results. These researchers used brain-imaging (positron emission tomography) instead of EEGs and cognitive-behavioral therapy instead of placebos. But once again this study reported brain changes that correlated with improvements in mood, and these physiologic changes differed according to the treatment received. With cognitive-behavioral therapy, some areas in the cortex became less active, whereas areas of the limbic system became more active, and with drug treatment metabolism in the cortex increased and it slowed in the limbic system. One author of the study, surprised by the findings, noted that antidepressants and cognitive-behavior therapy appear to have no “final common pathway.” Of course, if they had, we would not expect the most notable finding of this study: The effects of cognitive-behavior therapy on mood (by way of the brain) were significantly longer lasting than those of the drug.

Just as some antidepressants are better for some individuals than for others, might not some cases of depression, severe or

otherwise, be better suited for psychotherapy than drug therapy, or some cases be in need of both? Advances in medical practice require more than advances in basic and clinical science; they require identification and application to patients of the most effective treatments available. Cost and insurance coverage clearly place constraints on this treatment. Studies have shown, however, that although psychotherapy can be more costly at the outset, it can reduce costs of treatment by preventing relapses.<sup>3</sup> One such study, which appeared in the *British Journal of Psychiatry* in 1997, showed that cognitive therapy was as effective as pharmacologic treatment, both acutely and in a maintenance phase, and appeared to offer better long-term outcomes for clinical depression. A similar study, from the *Archives of General Psychiatry* in 1998, examined the long-term outcomes of individuals with recurrent depression. Over the course of 20 weeks, patients who responded to pharmacologic treatment were gradually tapered off the drugs. Half then received cognitive-behavioral therapy, and the other half received no therapy. Two years later, only 25 percent of the patients receiving cognitive-behavioral therapy had relapsed, whereas 80 percent of patients without any follow-up therapy had relapsed.

#### **BITTER OR BETTER?**

On October 30, 2003, the Associated Press reported that Lilly had obtained further approval for their forthcoming Cymbalta, noting that the drug could be a “potential blockbuster.” An earlier story, this one at *Forbes.com* (August 2003), made a similar claim, suggesting that “the new medicine is

a follow-up to Prozac that works by keeping the brain from reabsorbing serotonin, as most antidepressants do, but also by targeting the reuptake of norepinephrine, which drugs like Prozac ignore.” The story also noted that Cymbalta “is not the first drug to target both serotonin and norepinephrine—that honor goes to Effexor, a blockbuster made by Wyeth and put on the market around the same time as Prozac.”

Of course, Effexor, which is neither a tricyclic nor an SSRI, was not the first dual-action agent. Most of the tricyclic antidepressants were dual-action agents, including Lilly’s first antidepressant, nortriptyline. What this means is that not only have most reports missed the truth behind Lilly’s new drug—that it represents old technology, not new—but they have also failed to note the implication that little progress is being made in drug development for treating depression.

Indeed, no medications appear to be in the pipeline that represent any kind of advancement in treatment, nor is research being pursued by the drug makers that might lead to a breakthrough. Instead, the drugs available for depression continue to be variations on the same amine theme. Lilly’s circular rather than forward path from nortriptyline to Prozac to Cymbalta is a hardly promising trajectory, given the company’s prominence among psychopharmaceutical manufacturers. Yes, some of the newer drugs appear to be safer and perhaps more effective than others (notably, drugs that act more selectively on norepinephrine than serotonin), but, many experts agree, none mark a great deviation from a theory that first appeared 40 years ago.<sup>4</sup>

The SSRIs remain the dominant class of antidepressants today. Yet as the conclusion of a 1999 report from the Department of Health and Human Services states, “The SSRIs are no more effective at treating depression than older classes of drugs, like tricyclics.” But then, greater efficacy was not the initial claim for why the SSRIs were hailed as better than the tricyclics. Rather, it was that they resulted in fewer side effects—a fact that, were it indeed correct, would be highly problematic today for Lilly’s dual-action Cymbalta.

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But this claim about fewer SSRI side effects has, in fact, proven to be true in only one important respect: An overdose of SSRIs is less likely to cause harm or death than is an overdose of a tricyclic. The SSRIs do produce fewer minor side effects, such as dry mouth, than do the tricyclics. But such side effects pose no greater risk than do the various moderate-to-serious side effects of the SSRIs that are not associated with most tricyclics.

These SSRI side effects include problems of physical dependence, which can result in a withdrawal syndrome that is often worse

than the problem for which the drug was prescribed. They also include problems of lowered libido, which were at first deemed uncommon but have now been shown to be more likely to occur than not. A less common but even more serious problem, already noted with respect to reserpine, is that of akathisia—a syndrome involving agitation and turmoil that sometimes leads to suicide or even murder.<sup>5</sup> In 2003, evidence of increased suicide risk for children taking SSRIs led to a near total ban on their pediatric use in Britain. Warnings against use with patients younger than 18 were also made by the U.S. Food and Drug Administration in 2003. In 2004, both U.S. and British regulators expanded their investigation and warnings about akathisia and risk of violence to include the adult use of SSRIs. If Cymbalta looks like an improvement in this context, it is one achieved only by going backward, not forward.

Since the arrival of the SSRIs, something else has become noticeable: a widening gap between the clinical and scientific evidence about any particular antidepressant, on the one hand, and the popular acceptance of antidepressant drugs by physicians, the media, and the public, on the other. Such a gap raises a serious public health issue, one that is reinforced by Lilly’s failure to come forward with a truly innovative treatment. Clinical practice should be guided by science, yet it appears that the makers of antidepressants have learned a very different lesson. A company need only get a compound on the market, even if that requires dubious clinical trial data, and then it can turn on a marketing machine that essentially overshadows

the true merits and side effects of the drug. In such a marketplace, with direct television advertising and an army of sales representatives, drug makers need hardly do anything more than offer a placebo, even a toxic placebo, to generate annually hundreds of millions or even billions of dollars. It is ironic, meanwhile, that, as depression has been popularized by drug makers and the media, those who suffer it most gravely appear to have faded from view. ■

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