A. The Evidence Base for Antidepressants

Short-term use

Two classes of antidepressants, monoamine oxidase inhibitors (MAOIs) and tricyclics, were introduced in the late 1950s, and thus there is now 50 years of research literature on the short-term efficacy of antidepressants. The story told in that research literature regarding the short-term efficacy of these medications is fairly consistent.

By the 1970s, investigators had concluded that the MAOIs and tricyclics provided a modest benefit over placebo. In 1974, Morris reported that the antidepressant bested placebo in two-thirds of the studies that had been conducted.[i] In a 1975 review, Rogers found that 10 of 28 studies of imipramine (36%) showed a benefit for the drug-treated patients.[ii] The NIMH, in its 1969 review of the literature, determined that 61% of the medicated patients in well-controlled trials improved, versus 46% of the placebo patients, for a "net" drug benefit of 15%. "In well-designed studies," the NIMH concluded, "the differences between the effectiveness of antidepressant drugs are not impressive." [iii]

The modest efficacy of the first-generation antidepressants led some researchers in the 1970s to wonder whether the placebo response was the mechanism that helped many patients feel better. What the drugs did, several reasoned, was amplify the placebo response, and they did so because they produced physical side effects, which helped convince patients they were getting a "magic pill" for depression. To test this hypothesis, investigators conducted at least seven studies in which a tricyclic was compared to an active placebo (atropine), rather than an inert one. The active placebo produced a side effect of some type, such as dry mouth, and in six of the seven trials, there was no difference in outcomes.[iv]

During the 1970s and 1980s, the NIMH conducted at least two major studies of the tricyclic imipramine. In the first one, which was a study of hospitalized depressed patients, fewer than half of the drug-treated patients completed the seven-week trial, and the reason that so many dropped out was that their condition "deteriorated," or because they failed to improve. Although imipramine was superior to placebo in psychotically depressed patients, it did not show a benefit in "neurotic depressives."[v]

In the second study, which was part of the NIMH's large "Treatment of Depression Collaborative Research Program," imipramine was compared to two forms of psychotherapy and placebo. At the end of sixteen weeks, "there were no significant differences among treatments, including placebo plus clinical management, for the less severely depressed and functionally impaired patients." Only the severely depressed patients fared better on imipramine than on placebo.[vi]

Such was the record of short-term efficacy racked up by the tricyclics. These drugs appeared to provide a modest benefit, at least for certain subgroups of patients (those psychotically depressed and severely depressed). However, most studies that employed an active placebo failed to show a benefit for the drug.

When the SSRIs came to market in the late 1980s and early 1990s, they were touted as being markedly superior to the old tricyclics, and numerous studies appeared in the medical literature asserting their efficacy over placebo. But reviews of the clinical trial data submitted by the manufacturers of the SSRIs to the FDA told a different story.

In 2000, Khan reviewed the data submitted to the FDA for seven SSRIs and concluded that symptoms were reduced 42 percent in patients treated with tricyclics, 41 percent in the SSRI group, and 31 percent in those given a placebo. The SSRIs were no more effective than the old tricyclics.[vii]

Next, Turner reviewed FDA data for 12 antidepressants approved from 1987 to 2004, and he found that 36 of the 74 trials had failed to show a statistically significant benefit for the antidepressants. Twenty-two of the negative studies were never published, while in 11 other instances, the negative results were spun in the published articles to make it appear that the results were positive for the drug.[viii] This publication bias had created a false impression that the SSRIs regularly bested placebo in the trials.

Finally, in 2008, Kirsch reported that in trials of four SSRIs (Prozac, Effexor, Serzone, and Paxil), symptoms in the medicated patients dropped 9.6 points on the Hamilton Rating Scale of Depression, versus 7.8 points for the placebo group. This was a difference of only 1.8 points, and the National Institute for Clinical Excellence in Britain had determined that a three-point drug-placebo difference was needed on the Hamilton scale to produce a "clinically significant benefit." It was only in a small group of patients, those most severely depressed, that the SSRIs had been shown to be of real use. "Given these data, there seems little evidence to support the prescription of antidepressant medication to any but the most severely depressed patients, unless alternative treatments have failed to provide benefit," Kirsch concluded.[ix]

In sum, after 50 years, there is evidence that antidepressants provide a short-term benefit compared to placebo for severely depressed patients. However, there isn't good, consistent evidence that they regularly provide a clinically meaningful short-term benefit to patients with mild to moderate depression. It also isn't clear that antidepressants are more effective over the short term than "active placebo."

Maintenance use of antidepressants

The evidence for long-term use of antidepressants comes from drug-withdrawal studies. In these studies, patients who had stabilized well on an antidepressant were either maintained on the drug, or withdrawn from it. In a 2003 analysis, Geddes reported that in 31 studies involving 4,041 patients, 41% of the drug-withdrawn patients relapsed versus 18% of the drug-maintained patients, with most of these studies lasting twelve months.[x]

B. The Effect of Antidepressants On Long-term Outcomes

The maintenance studies do not reveal how antidepressants are altering the long-term course of depression. They do show that once patients are on the medications, there is a high risk of relapse when they come off. But that high risk may be due to drug-withdrawal effects, and thus there is a need to try to flesh out whether the medications offer a benefit over the long term.

There is a long-running concern in the long-term outcomes literature that the medications may increase the chronicity of the disorder. That concern has been raised most notably by Giovanni Fava, editor of *Psychotherapy and Psychosomatics.* And in this paper, we are seeking to review the long-term outcomes data to see if that concern is warranted. The first step in this review is fleshing out, as best as possible, the "natural" course of unmedicated depression in the pre-pharmacotherapy era.

The long-term course of depression prior to the "antidepressant" era

Prior to the 1960s, patients with "unipolar depression" were regularly studied as part of a larger "manic-depressive" cohort. However, it is possible to dig into the manic-depressive studies and identify the "depressed" only patients.

In the first decades of the 20th century, German psychiatrist Emil Kraepelin followed 450 "depressed only" hospitalized patients, and he found that over the long-term, 60% experienced but a single bout of depression, and only 13% had three or more episodes.[xi] He found similar outcomes in his manic patients, which led him to conclude that manic-depressive illness had a favorable long-term course. "Usually all morbid manifestations completely disappear; but where that is exceptionally not the case, only a rather slight, peculiar weakness develops," he wrote in 1921.[xii]

Other investigations produced similar results. Pollock, in a long-term study of 2,700 depressed patients hospitalized in New York from 1909 to 1920, found that more than half of those admitted for a first episode had but a single attack, and only 17 percent had three or more episodes.[xiii] In Sweden, Lundquist followed 216 patients hospitalized for depression for 18 years, and he determined that 49% never experienced a second attack, and that another 21 percent had only one other episode. In total, 76 percent of the 216 patients became "socially healthy" and resumed their usual work.[xiv]

These good long-term outcomes spilled over into the first years of the antidepressant era. In 1972, Guze determined that in follow-up studies that lasted 10 years, 50% of people hospitalized for depression had no recurrence of their illness. Only 10% became chronically ill.[xv]

Given these outcome studies, NIMH officials and academic psychiatrists in the 1960s and early 1970s regularly described depression as having a good long-term course. "Depression is, on the whole, one of the psychiatric conditions with the best prognosis for eventual recovery with or without treatment. Most depressions are self limited," Cole wrote in 1964.[xvi] Observed Kline that same year: "In the treatment of depression, one always has an ally the fact that most depressions terminate in spontaneous remissions."[xvii]

Winokur, in his 1969 book *Manic Depressive Illness*, advised the public that "assurance can be given to a patient and to his family that subsequent episodes of illness after a first mania or even a first depression will not tend toward a more chronic course."[xviii]

The changing long-term course of depression

Shortly after the introduction of MAOIs and tricyclics, several European psychiatrists observed that the long-term course of depression in their drug-treated patients seemed to be changing. Exposure to antidepressants, wrote Hoheisel in 1966, appeared to be "shortening the intervals" between depressive episodes. The drugs, reported a Yugoslavian doctor in 1970, were causing a "chronification" of the disease. The tricyclics, Schipkowenski noted that same year, were inducing a "change to a more chronic course."[xix]

With this concern having surfaced, a Dutch psychiatrist, J.D. Van Scheyen, examined the case histories of 84 depressed patients. Those who had not taken an antidepressant had fared better over a five-year period. "It was evident, particularly in the female patients, that more systematic long-term antidepressant medication, with or without ECT, exerts a paradoxical effect on the recurrent nature of the vital depression. In other words, this therapeutic approach was associated with an increase in recurrent rate, and a decrease in cycle duration . . . Should [this increase] be regarded as an untoward long-term side effect of treatment with tricyclic antidepressants?"[xx]

Over the next 20 years, numerous researchers reported that drug-treated patients relapsed at high rates when they withdrew from an antidepressant. In a 1997 review, Viguera reported that in the first few months following withdrawal, monthly relapse rates averaged 6.24%, with 50% of all drug-withdrawn patients relapsing within 14 months. Viguera also found that the longer the patients had been on an antidepressant prior to withdrawal, the higher the relapse rate.[xxi]

This high relapse rate for drug-withdrawn patients is what provides the evidence for long-term use of antidepressants. But when viewed through a historical lens, we see that prior to the use of antidepressants, a high percentage of patients hospitalized with major depression spontaneously recovered, and many then remained well for long periods. The high relapse rate for non-medicated patients is seen in drug-exposed patients, and not necessarily in drug-naïve patients.

In addition, the relapse studies were conducted primarily in good responders to antidepressants (those who had remitted), and thus the stay-well rate for the drug-maintained patients in those maintenance studies does not accurately reflect the stay-well rate for all patients initially treated with antidepressants.

Summaries of modern outcomes for people who experience an initial bout of major depression describe an illness that tends to run a chronic course. One-third of unipolar patients do not respond to an antidepressant, even over the short-term, and this group is said to have a poor long-term outcome. Another third are partial responders—i.e. their

symptoms decrease over the short-term but do not remit. This group also fares poorly over the long-term.[xxii] "Resolutions of major depressive episode with residual subthreshold depressive symptoms, even the first lifetime episode, appears to be the first step of a more severe, relapsing, and chronic future course," Judd concluded in a 2000 report.[xxiii] Finally, some of those who remit and continue to take medication still relapse.

The 1999 edition of the American Psychiatric Association's *Textbook of Psychiatry* summarized the outcomes literature in this way: "Only 15% of people with unipolar depression experience a single bout of illness," and for the remaining 85%, with each new episode, remissions become "less complete and new recurrences develop with less provocation."[xxiv]

Two recent studies highlight the chronic nature of unipolar depression today. First, in 2004, Rush observed that clinical trials cherry-picked patients most likely to respond well to an antidepressant, as patients with co-morbidities and other complicating factors were regularly excluded. "Longer-term clinical outcomes of representative outpatients with nonpsychotic major depressive disorder treated in daily practice in either the private or public sectors are yet to be well defined," he wrote. To fill in his gap, Rush treated 118 "real-world" patients with antidepressants and provided them with emotional and clinical support "specifically designed to maximize clinical outcomes." However, only 26% responded to the antidepressant (meaning that their symptoms decreased at least 50% on a rating scale), and only about half of those who responded stayed better for any length of time. Only 6% of patients remitted and stayed well throughout the yearlong trial. These "findings reveal remarkably low response and remission rates," Rush concluded.[xxv]

Rush was also one of the lead investigators in the NIMH's STAR*D trial, which was the largest antidepressant trial ever conducted. Although published reports and NIMH press releases indicated that two-thirds of the 4,041 patients entered into the trial eventually remitted (after multiple trials of medication), Pigott and others who have critically analyzed the published data have found that the actual results were much more dispiriting. There were 3,110 patients who began the study with a Hamilton score ≥ 14 and thus, according to the protocol, were depressed enough to be eligible for enrollment, and 1,192 of that group (38%) remitted during one of the four stages of treatment (Hamilton score ≤ 7).[xxvi] Only 108 of all 4,041 patients remitted and stayed well throughout the year-long followup. Thus, the documented stay-well rate in the STAR*D study, even including those patients whose initial depression was too mild to qualify them for the study, was 3%. The remaining 97% either failed to remit, relapsed, or dropped out.[xxvii]

It's clear from this historical review that researchers' understanding of the course of depression has changed during the antidepressant era, from an episodic disorder into a more chronic one. The usual explanation for this noted change in outcomes is that the old epidemiological studies must have been flawed. It used to be thought that "most patients would eventually recover from a major depressive episode," notes the 1999 edition of the American Psychiatric Association's *Textbook of Psychiatry.* "However, more extensive studies have disproved this assumption."[xxviii]

Are antidepressants depressogenic over the long-term?

In 1994, Fava penned an editorial in *Psychotherapy and Psychosomatics,* titled "Do antidepressant and antianxiety drugs increase chronicity in affective disorders?" that offered a different explanation for this change in outcomes.[xxix] Fava has revisited this question numerous times since then. He argues that antidepressants may cause "irreversible receptor modifications" that "sensitize" the brain to depression, and that this would explain the "bleak long-term outcome of depression" today. The use of antidepressant drugs, he wrote, "may propel the illness to a more malignant and treatment unresponsive state." [xxx]

His concern has been echoed by others. Baldessarini wrote that Fava's hypotheses "are not pleasant to contemplate and may seem paradoxical, but they now require open-minded and serious clinical and research consideration."[xxxi] El-Mallakh and others observed that "it is possible that antidepressant agents modify the hardwiring of neuronal synapses [which] not only render antidepressants ineffective, but also induce a resident, refractory depressive state."[xxxii]

There are no long-term randomized studies that can shed light on this possibility. But there are a handful of long-term naturalistic studies that do. The caveat with such studies is that at the time of initial diagnosis, it may be that the unmedicated group isn't as ill as the medicated group. It's also possible that those who eschew drugs have a greater "inner resilience." Even so, these naturalistic studies should provide insight into the long-term course of unmedicated depression today, and how it compares with the long-term course of medicated depression.

- In a retrospective study of the ten year outcomes of 222 people who had suffered a first episode of depression, Dutch researchers found that 76% of the unmedicated patients recovered and never relapsed, compared to 50% of those prescribed an antidepressant.[xxxiii]

- In a five-year study of 9,508 depressed patients, Canadian researchers found that the medicated patients were depressed on average 19 weeks a year, versus 11 weeks for those not taking antidepressants.[xxxiv]

- In a study designed to assess the value of screening for depression, which was conducted in 15 cities around the world, the World Health Organization reported that the 484 depressed patients who weren't exposed to psychiatric medications had better one-year outcomes than the 256 patients who were. The non-medicated patients enjoyed better "general health," their depressive symptoms were milder, and they were less likely to be judged still "mentally ill."[xxxv]

- Health officials in Ontario, Canada identified 1,281 people who went on short-term disability between 1996 and 1998 because they missed ten consecutive days of work due to depression, and found that those who subsequently didn't fill a prescription for an antidepressant returned to work, on average, in 77 days, while the medicated group took 105 days to get back on the job. Nine percent of the unmedicated cohort went on to long-term disability, compared to 19% of those who took an antidepressant.[xxxvi]

- In an NIMH-funded study, Coryell studied the six-year outcomes of 547 people who suffered a bout of depression, and he found that those who were treated for the illness were three times more likely than the untreated group to suffer a "cessation" of their "prinicipal social role," and nearly seven times more likely to become "incapacitated."[xxxvii]

- To assess the long-term course of unmedicated depression today, Posternak identified 84 patients enrolled in the NIMH's Psychobiology of Depression who, after recovering from an initial bout of depression, subsequently relapsed but then did not go back on medication. Although these patients were not a "never-exposed" group, Posternak could still track their "untreated" recovery from this second episode of depression. Twenty-three percent recovered in one month, 67% in six months, and 85% within a year. These results, Posternak concluded, were consistent with Kraepelin's observation that untreated depressive episodes usually cleared up within 6 to 8 months.[xxxviii]

A study by Blumenthal also sheds some light on this question. One hundred fifty-six elderly depressed patients were treated with an antidepressant (Zoloft), or an antidepressant plus exercise, or exercise alone. At the end of 16 weeks, those treated with exercise alone were doing as well as those in the other two groups. Blumenthal then followed the patients for another six months, during which time the patients were free to choose whatever treatment they wanted, and at the end of that time the patients treated initially with exercise alone were doing the best. Only 8% of those who had been well at the end of sixteen weeks relapsed during the follow-up, and by the end of ten months 70% of the exercise-only group were asymptomatic. In the two Zoloft-exposed groups, more than 30% of the patients who had been well at the end of 16 weeks relapsed, and fewer than 50% were asymptomatic at the end of ten months.[xxxix]

Together, these studies tell of unmedicated depression today running a fairly benign long-term course, with high recovery rates. The medicated patients in these studies experienced more depressive symptoms, lower recovery rates, and a greater risk of becoming disabled by the disorder.

C. SSRI Side Effects

The above review focuses on the effect that antidepressants have on the target symptom of depression, and to a certain extent, their effect on disability rates. In any risk-benefit

analysis, the drug is expected to have a positive effect on the target symptom, with this benefit outweighing the risks from side effects. Over the long-term, antidepressants do not appear to provide any such benefit (and in fact may worsen the long-term course of depression), and thus what is left in this risk-benefit analysis is summing up the drugs' adverse effects.

While the SSRIs may have a better safety profile than the tricyclics, they still cause a diverse array of side effects. These include nervousness, anxiety, muscle tics, suppression of REM sleep, nausea, diarrhea, gastrointestinal problems, anorexia, sexual dysfunction, emotional blunting, and apathy.[xl] In addition, investigators have reported that long-term use is associated with memory impairment, problem-solving difficulties, loss of creativity, and learning deficiencies.[xli]

Antidepressants also increase the risk that a depressed person will convert to bipolar illness. Martin reviewed the records of 87,290 patients diagnosed with depression or anxiety between 1997 and 2001 and determined those treated with antidepressants converted to bipolar at the rate of 7.7% per year, which was three times greater than for those not exposed to the drugs. [xlii] As a result, over longer periods, 20% to 40% of all patients initially diagnosed with unipolar depression today eventually convert to bipolar disorder, which represents a worsening of their original illness.[xliii]

Finally, animal studies have raised worries about long-term use. Rats fed high doses of SSRIs for four days ended up with neurons that were swollen and twisted like corkscrews.[xliv] Other reports suggest that the drugs may reduce the density of synaptic connections in the brain, shrink the thalamus, trigger abnormalities in frontal lobe function, and deplete serotonin levels in the brain.[xlv] None of these concerns have been well-studied or documented, but together with reports that long-term use is associated with cognitive impairment, they suggest that the drugs may have a deleterious effect on brain function over time.

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