COMMENTARY

Are Antidepressants Effective in the Acute and Long-term Treatment of Depression? *Sic et Non*

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ABSTRACT

The efficacy of antidepressant treatment of major depression remains a matter of controversy. A review of acute treatment studies suggests that for relatively more severe episodes of major depression, antidepressants are superior to treatment in the "placebo group;" however, there are numerous methodological confounds in the available literature. (Some recent, preliminary evidence suggests that antidepressants may also be of benefit in some less severely depressed populations).

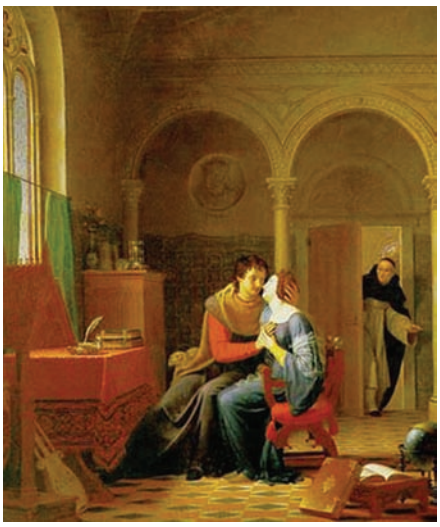
There is moderately strong evidence that, compared with placebo, maintenance antidepressant treatment reduces six-month relapse rates in major depression; however, it is less clear that antidepressants prevent actual recurrence of depression in the longer term. There is evidence of both over-use and under-use of antidepressant treatment, and there appears to be a "mismatch" between diagnosis and optimal treatment of depression in some clinical settings. Better designed studies are needed to resolve these uncertainties and to investigate such putative conditions as "oppositional tolerance" to long-term antidepressant treatment. The author advocates a conservative approach to antidepressant treatment, as well as a substantially extended "tapering" period when antidepressants are discontinued.

INTRODUCTION

"By doubting we come to examine, and by examining we reach the truth." —*Peter Abelard*

Where is Peter Abelard (1079–1142), now that we need him? The recent flurry of articles, letters, and blogs about antidepressants[1–3] surely cries out for the brilliant author of *Sic et Non*, wherein Abelard presented 158 questions with seemingly contradictory answers from various theologians. Abelard did not try to harmonize these "yes and no" answers, but he suggested ways in which they could be harmonized—for example, by looking carefully at the definitions of words and checking the context of the citation.

In the matter of antidepressants, we can apply Abelard's method to the seemingly contradictory claims from various "experts" (and many non-experts), in hopes of arriving at reasonable synthesis of the data. In that spirit, I pose three key questions



Abaelardus and Heloïse surprised by Master Fulbertby —Jean Vignaud [illustration courtesy of Wikipedia]

in this commentary and attempt to provide viewpoints from both the "yes" and "no" perspectives.

QUESTION 1. Do we have convincing evidence that antidepressants are more effective than placebo for the acute treatment of major depression?

Yes. Multiple, placebo-controlled studies and meta-analyses have shown that, on average, antidepressants are significantly more effective than placebo, in the *acute* treatment of major depressive disorder (MDD).

No. Several meta-analyses and many placebo-controlled studies of MDD have shown, on the whole, very little efficacy for antidepressants as compared with placebo.

Discussion. Well, as Abelard would observe, so much depends on the meaning of our terms, e.g., *convincing, effective, significantly, efficacy, placebo,* and *major depression* (The construct of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*]'s major depressive episode is about as broad and meandering as the Mississippi). The standard "textbook" teaching—allowing for many differing texts—is that, in general, acute antidepressant monotherapy leads to remission in about 40 percent of patients in placebo-controlled trials, compared with about a 25-percent remission rate with placebo. This is a respectable, but not spectacular, difference. But even these figures have been called into question recently. Why?

First, many of the largest studies have been sponsored by pharmaceutical companies, which often raises questions about biased interpretation and unpublished, "negative" studies. But there are more subtle issues. Sometimes, what convinces a statistician will not convince a clinician—or a patient. For example, a change in two points on the Hamilton Depression Rating Scale (HDRS) may be *statistically* significant in an antidepressant study, but of only marginal clinical significance. Moreover, the HDRS itself is subject to variability, depending on the level of experience of the rater: poorly-trained raters tend to produce results that diminish the effect of the antidepressant.[4]

Meta-analyses are subject to several criticisms along the lines of "garbage in, garbage out" and publication bias (e.g., failure to include unpublished, negative studies). Moreover, in some supposedly double-blind studies of antidepressants, subjects and/or researchers are able to discern the active treatment, which tends to bias the study in favor of the antidepressant. On the other hand, some meta-analyses of antidepressant treatment have included studies with suboptimal antidepressant dosing,[5] which would tend to reduce drug-placebo differences.

There is also much misunderstanding, especially in the lay press, of what the term *placebo* really means. As Dr. Sheldon Preskorn has observed, in a typical eight-week trial, a subject in the so-called placebo group may receive 10 to 12 hours of supportive contact time with knowledgeable and empathic healthcare practitioners (personal communication, 2/3/10). Indeed, the actual comparison in such studies is between *medication plus supportive care*, versus *placebo tablet plus supportive care*. This supportive intervention—though not a form of psychotherapy—is hardly the equivalent of swallowing a "sugar pill," which is the usual characterization of the placebo in many nonprofessional publications. Now, it is perfectly true that both the placebo (PBO) and active medication group (MED) get all this attention in a typical study; so, in theory, it ought to be "a wash," with the two interventions cancelling out and leaving us with a clear comparison of the specific MED effect with the "sugar pill" (PBO). But this assumes that there is no interaction or "synergy" between the PBO pill and all the attention, support, and "tender loving care" (TLC)—perhaps producing a total effect that is greater than the sum of its parts. We really do not know whether this occurs or not, but it remains the case that nobody has literally studied MED vs. PBO in depression, *apart from the environment of the clinical study's support, empathy, and education*. We therefore have no reason to infer from these studies that if a doctor simply gave a depressed patient a sugar pill or vitamin and sent her out the door, that in six weeks the patient would show as much improvement as PBO subjects in a clinical study. In short, in clinical studies, there is far more than a "sugar pill" involved, and we cannot assume that the results reflect the inherent power of the sugar pill versus the active drug.

All that said, most mood disorder experts would acknowledge that many randomized studies do not show a large difference in MED versus PBO outcomes in cases of *mild-to-moderate* depression (Please see Sidebar Note on the following page for recent exceptions added to this article after it was peer reviewed and accepted for publication.)

There are other reasons why results from antidepressant studies often do not square with the experience of many clinicians. As

Brown has pointed out, participants in randomized, controlled trials (RCTs) are usually not representative of the general population of depressed patients (W.A. Brown, personal communication, 8/8/11). For example, RCT subjects are generally excluded if they are suicidal or have significant psychiatric comorbidity. Moreover, placebo response rates in RCTs have been rising in recent years[6]—perhaps owing, in part, to recruitment of less severely ill subjects for study. The less ill the subjects, of course, the more likely a placebo is going to work for them. Placebo response rates also vary in relation to the number of sites involved in a study, perhaps because with more sites, it becomes more difficult to maintain strict entry criteria. Thus, Bridge et al[7] concluded that "…the recent shift toward large multisite trials of antidepressant medications for pediatric major depression may be contributing to an increasing incidence of response to placebo." In short, with respect to antidepressant efficacy, it is difficult to extrapolate from the results of RCTs to what clinicians observe in everyday practice.

Finally, the construct of "major depressive disorder" (MDD) is so elastic, it could be stretched around almost anyone with depressive symptoms or loss of pleasure, accompanied by significant distress or impairment. For example: Ms. Smith may meet MDD criteria based on two weeks of symptoms, and no previous episodes; whereas Mr. Jones meets MDD criteria based on *two years* of symptoms and *five* previous episodes. Furthermore, if we don't control for the *melancholic* subtype of MDD, we may not be giving the antidepressant a "fair shake." Why? Because most data suggest that the *melancholic subtype*—not simply the *severity* of the depression—predicts a better

response to antidepressants, as compared with placebo or psychotherapy.[8]

Synthesis. All this said, it is nevertheless true that acute antidepressant response rates in some large studies (such as the STAR*D) have been unimpressive.[9,10] I would suggest that, in the aggregate, the antidepressants we now have are just "so-so" as acute treatments—by no means worthless and sometimes very helpful (as in severe, melancholic depression), but not robustly effective medications across the board. Nor do combinations of these drugs, when given as "first-step" treatment, seem as helpful as we once thought or supposed, based on the recent CO-MED study.[11]

Psychopharmacologists should not be too surprised by these downbeat findings, since we are using a good many "me too" drugs,[10] which are agents that are thought to work by revving up one or two monoamine neurotransmitters (though this putative mechanism of action is certainly an oversimplification).

We clearly need more creative approaches to the pharmacotherapy of depression, such as agents that affect the N-methyl-D-aspartic acid (NMDA) system. Thus, recent promising studies of the anesthetic agent, ketamine, for acute depression[12] need to be refined and expanded to safer agents that work through the NMDA and other neuromodulatory systems. Nevertheless, I believe the evidence is good enough to justify prescribing antidepressants for the acute treatment of patients with severe, and especially, melancholic major depression.[8,13]

And finally, our logician, Peter Abelard, would insist that critics cannot have it both ways, i.e., claiming that antidepressants are no better than "sugar pills" while acknowledging that these agents outperform placebo in cases of severe and melancholic depression.[5,8,15]

QUESTION 2. Do we have convincing evidence that antidepressants are more effective than placebo for the long-term, *maintenance* treatment of major depression?

Yes. Maintenance studies comparing AD to placebo have repeatedly shown that antidepressants provide significantly better protection against relapse, and perhaps recurrence, of major depression.

No. Maintenance studies generally show only a modest benefit for antidepressants versus placebo, mainly in the first six months after the index episode, and only for the relatively small subgroup of patients who remain in treatment.

SIDEBAR NOTE

The followoing are two recent exceptions to the general consensus that many randomized studies do not show a large difference in MED versus PBO outcomes in cases of mild-to-moderate depression.

1. Stewart et al[a] analyzed six placebo-controlled antidepressant studies of patients with nonsevere MDD (Hamilton Depression Score <23) and found that "mild-moderate MDD can benefit from antidepressants," with the NNT (number needed to treat) in the range of 3 to 8 (NNT<10 is considered clinically significant).

2. In a re-analysis of the United States Food and Drug Administration database studies previously analyzed by Kirsch et al, Vöhringer and Ghaemi[b] concluded that antidepressant benefit is seen not only in severe depression but also in moderate (though not mild) depression.

[a] Stewart JA, Deliyannides DA, Hellerstein DJ, McGrath PJ, Stewart JW. Can people with nonsevere major depression benefit from antidepressant medication? *J Clin Psychiatry.* 2012 Apr;73(4):518-25. Epub 2011 Dec 27.]

[b] Vöhringer PA, Ghaemi SN. Solving the antidepressant efficacy question: effect sizes in major depressive disorder. *Clin Ther.* 2011 Dec;33(12):B49-61. Epub 2011 Dec 2.

Discussion. There are numerous randomized, placebo-controlled studies that find antidepressants superior to placebo in preventing (unipolar) depressive relapse. Based on his review of the literature up through the mid-1990s, Sheldon Preskorn opined that "…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."[16] There have now been randomized, double-blind, placebo-controlled studies showing that sertraline,[17] venlafaxine,[18] nefazodone,[19] and other antidepressants are significantly more effective than placebo in preventing depressive relapse and/or "recurrence," over periods of up to two years. (I have put quotations around the term *recurrence* for reasons that will soon be clear).

At first blush, these findings seem quite convincing, but some experts are not greatly impressed by the maintenance data. For example, as Ghaemi has noted in a careful reanalysis of the STAR*D maintenance data,[20] only a quarter of the overall sample maintained their remission after one year—not an impressive figure. Now, the STAR*D lacked a placebo control. But in his assessment of placebo-controlled maintenance studies, Ghaemi argues that "….efficacy greater than placebo does not mean efficacy in most persons" and that "the actual effect size of long-term absolute benefit is small."[20] Here's another way of putting it: a 2-point improvement on a few HDRS items is not the same as "getting your life back" from major depression. Very few studies of maintenance treatment look, for example, at quality of life, social relationships, and ability to rejoin the work force.

There is another problem that bedevils many placebo-controlled maintenance studies. For example, the Kornstein et al two-year study[18] of venlafaxine concluded that "... patients with recurrent MDD *who respond to antidepressant treatment* obtain substantial benefit from ongoing preventive therapy," (italics added). But herein lies a conundrum: As Ghaemi has pointed out, in the typical maintenance study, it is only the medication responders who are retained in the study and randomized to the maintenance phase. Sometimes termed an *enriched* design, this procedure might be described, more cynically, as "cherry picking" your patients. Those who do not respond or remit on acute antidepressant treatment are weeded out of the maintenance phase of study.

Aside from the entry criteria for RCTs discussed earlier, the enriched design does not really allow us to generalize to the wider population of depressed patients we see in clinical practice. As Ghaemi puts it, "The problem is that once you preselect completers [for maintenance drug treatment], people who have stayed in the study at 1 year, you no longer have a randomized sample, and this approach always favors drug," (S.N. Ghaemi, personal communication, 8/3/11). Furthermore, in this sort of *enriched* design study, progressively smaller cohorts move through each stage of the protocol, such that the results at the end apply to a small and very select group. Thus, in a re-analysis of the Kornstein et al two-year study,[18] Ghaemi found that at 18 months into the study, only a little over 18 percent (131/715) of the initial sustained responders remained well (Ghaemi SN, personal communication, 8/4/11).

Furthermore, Ghaemi has been critical of certain design flaws that fail to distinguish between "relapse" and "recurrence." Based on the natural history of most major depressive episodes, those occurring within six months of the index episode most likely represent a *relapse* of the original episode—not a recurrence. Thus, in Ghaemi's view, true prophylaxis of mood episode recurrence should entail medication benefit for *six months or longer after resolution of the index mood episode*.[21]

To explore this issue, Briscoe and El-Mallakh[22] reviewed 16 randomized, double-blind, placebo-controlled trials in which the combined duration of the continuation and maintenance phases was at least 18 months or longer. Analyzing Kaplan-Meier survival curves, the authors found that, indeed, patients continued on antidepressants experienced a lower rate of depression relapse than patients switched to placebo by study end in the vast majority of maintenance studies. However, closer analysis of the survival curves and original data revealed that much of the difference in survival resulted from a disproportionate rate of relapse (63–100%) that occurred in the placebo arms within the first six months of the studies. There did not appear to be a difference in the proportion of depression recurrence (placebo vs. antidepressant) after the first six months in the vast majority of maintenance trials reviewed. The authors concluded that, "These findings may challenge the hypothesis that antidepressants provide prophylaxis against depressive episodes."[22] These as yet unpublished findings will of course require replication and further analysis.

The maintenance antidepressant story gets even more complicated. Some researchers have expressed concern for possible delayed ("tardive") dysphoria associated with long-term antidepressant use, while others have argued that long-term antidepressant use may alter brain function in deleterious ways.[23,24] Andrews et al[24] recently published a meta-analysis that examined both "extension" and "discontinuation" studies of antidepressant treatment. In brief, in extension studies, patients diagnosed with MDD are initially randomly assigned to antidepressant or placebo during the treatment phase, and then remitters in both groups are followed in an extension phase in which they continue to receive the same treatment. In discontinuation studies, all patients diagnosed with MDD go through an initial antidepressant *treatment*

phase and then remitters go through a *discontinuation phase* in which they are randomly assigned, under double-blind conditions, to either continued treatment (drug-drug) or placebo (drug-placebo). The Andrews et al study[24] appeared to show that "…the risk of relapse after ADM *discontinuation* was higher than the risk of relapse after remission on placebo." (italics added)

The authors went on to argue that chronic antidepressant treatment may lead to "oppositional tolerance" to antidepressants. This hypothesis posits that the brain "pushes back" against the chronically-administered antidepressant, such that when the medication is stopped, the brain tends to "overshoot" its normal chemical equilibrium. (Think of a compressed spring that is suddenly released from pressure). This, the authors maintain, leaves the patient more vulnerable to depressive relapse than someone who had never taken the antidepressant in the first place.

Synthesis. How do we reconcile these opposing views and studies? How do we assess the claims of those who argue that long-term antidepressant treatment may do more harm than good?

First, we need to realize that studies of antidepressants are susceptible to a multitude of variables, both controllable and uncontrollable. For example, one of many possible confounds is the *number of prior depressive episodes* of the subjects under study. Thus, in a review of all published randomized, placebo-controlled, double-blind clinical trials, Kaymaz et al[25] found that "antidepressants robustly reduce relapse risk in the maintenance phase…[but] there is evidence…that with increasing number of episodes, patients develop a relative resistance against the prophylactic properties of antidepressant medication." (Is it possible that this phenomenon is related to the putative "oppositional tolerance" hypothesized by Andrews et al? It is probably too soon to speculate on this). But this would suggest that the long-term benefits of antidepressant medication may depend, in some measure, *on the depressive history of the subjects under study*. Thus, if the active treatment and placebo groups are not carefully matched with respect to the *number of depressive episodes per patient*, inter-group comparisons may be misleading. Furthermore, a study's outcome could be skewed even by such subtle (and hard to detect) factors such as the number of depressed outpatients who were taking *over-the-counter non-steroidal anti-inflammatory drugs*, such as ibuprofen. Recent research has shown that NSAIDs may interfere with SSRI-antidepressant effects.[26]

Finally, *psychodynamic factors* may also affect placebo responsiveness and, hence, drug-placebo differences. For example, patients who are highly motivated to change and receive a placebo may show greater change in symptoms than patients who receive the active drug but who are less ready to change.[27] It hardly needs saying that no large, randomized antidepressant trials have examined such fine-grained psychological issues.

Despite these various confounds, some experts find robust evidence of long-term preventative effects of antidepressants. Thus, in a recent comprehensive review, Davis et al[28] conclude as follows:

"There is no indication that the relapse rate from antidepressant therapy increases with the duration of treatment. In other words, antidepressants provide effective prophylaxis against relapses. Since the drug either prevents or delays relapse, patients will spend less of their lifetime in a depressive episode. Long-term morbidity and disability can be diminished by treatment."[28]

And, while the enriched design discussed above tends to favor active drug over placebo, it is nevertheless true that, in clinical practice, the only patients we place on maintenance treatment with drug A are the ones who responded acutely to drug A.

With regard to the possibility of "tardive dysphoria"—a delayed "pro-depressant" effect—this could be a real phenomenon in a small subgroup of chronically treated patients with major depression. However, it is hard to disentangle what El-Mallakh et al[23] call tardive dysphoria from an inherent worsening, or re-emergence, of the patient's illness for non-pharmacological reasons (i.e., late-onset "dysphoria" may simply represent the "natural history" of the illness in a subgroup of depressed individuals or the effect of undetected psychosocial stressors). We will need carefully controlled, longitudinal studies to sort out these possibilities.

As for the provocative study by Andrews et al,[24] there appear to be both methodological and conceptual problems with the Andrews et al analysis. Recall their main conclusion that "…the risk of relapse after ADM discontinuation was higher than the risk of relapse after remission on placebo." But this comparison is questionable, for several reasons (M. Thase, MD, personal communication, 7/28/11). For one thing, subjects in the extension studies had different initial expectations than those in the discontinuation studies; e.g., subjects entering the placebo extension studies knew that their treatment was not going to change, whereas all of the patients in the antidepressant discontinuation studies knew there was a good chance they that might wind up receiving a placebo for continuation or maintenance phase therapy. More important: subjects in the extension studies who *remitted on placebo* may have been an inherently less "sick" group—for example, containing fewer subjects with melancholic features—than the group that had achieved remission on antidepressants in the discontinuation studies. This phenomenon is known as the "differential sieve effect" and reflects different "susceptibility biases" for the two groups (A. Nierenberg, MD, personal communication, 7/26/11; M. Thase, MD, personal communication, 7/28/11). Furthermore, as Davis has

pointed out, the Andrews et al meta-analysis evaluates and compares studies from *vastly different time periods*, which very likely means that subjects entering the older studies were less placebo-responsive than those entering more recent ones (John M. Davis, MD, personal communication, 8/31/11).

Second, the monoamine-based theory of depression put forth by Andrews et al[24] (e.g., "…depressive symptoms are under monoaminergic control…") was long ago superseded by more sophisticated hypotheses[29] and is essentially a vestige of the "chemical imbalance" canard trenchantly critiqued by Valenstein[30] and, recently, by the present author.[31] Modern hypotheses of depression generally view monoamines as modulators of more primary neurobiological systems, such as dysfunctional signaling in specific neurocircuits. For example, reduced 5-HT(1B) heteroreceptor function may contribute to dysfunctional reward signaling within the striatum and may interact with non-aminergic neurotransmitters, such as GABA and glutamate.[32] The role of inflammatory cytokines[33,34] and nerve growth factors, such as BDNF[35,36] has also been emphasized in recent theories of depression. A corollary of this research holds that antidepressants, rather than simply increasing monoamines, may have important effects on the immune system and various neurotrophic factors.[36] For all these reasons, it may be argued that the Andrews et al study[24] is predicated on an oversimplified and outdated set of neurobiological assumptions.

That said, the Andrews et al[24] findings raise the possibility that "oppositional tolerance" to long-term antidepressant treatment may occur in at least some patients. This thesis was supported in a recent review by Fava and Offidani.[37] These authors opine that, "When we prolong treatment over 6 to 9 months we may recruit processes that oppose the initial acute effects of antidepressant drugs (loss of clinical effects)." This issue clearly requires further study (i.e., assuming the hypothesis is correct, are there discernable risk factors that could help us predict which subgroup of depressed patients are likely to develop such tolerance?)

More immediately, in my view, the Andrews et al study[24] raises the possibility that *rapid discontinuation* of antidepressants may leave some patients in a state of neurochemical "vulnerability" or disequilibrium. This could indeed reflect some kind of compensatory brain adaptation to long-term use of the antidepressant. However, as Dr. Vladimir Maletic noted, "…it is *interruption* [of antidepressant treatment] that may be the culprit." (V. Maletic, personal communication, 8/23/11; italics added). We see analogous phenomena in other areas of medicine (e.g., it has long been known that patients with ischemic heart disease may be susceptible to an acute exacerbation of their cardiac disease when beta-blocker treatment is *suddenly* stopped).[38] This does not mean that beta blockers are not useful in the long-term management of cardiac disease; it means that *rapid discontinuation* is a bad idea.

The same may apply in antidepressant treatment, but we may need to revise what we understand by the term *rapid discontinuation*. In my own practice, I would typically "wean" a patient off a chronically administered antidepressant over a period of *3 to 6 months* and sometimes longer. To my knowledge, this period of tapering has rarely, if ever, been used in existing studies of antidepressants or in routine clinical practice. In principle, longer periods of drug tapering might overcome the putative "oppositional tolerance" hypothesized by Andrews et al and by Fava and Offidani.[24,37]

In addition, we urgently need animal models and human biomarkers of both depression and its response to acute and chronic antidepressant treatment. Several candidate biomarkers are suggested by recent animal models.[39,40] Measures of brain-derived neurotrophic factor (BDNF) may prove useful in tracking response to antidepressant treatment (e.g., decreased serum levels of BDNF in antidepressant-naïve, depressed patients returned to normal in association with recovery from depression and antidepressant treatment).[36] One intriguing study suggests that elevated levels of C-reactive protein may predict good long-term outcome with antidepressant treatment but poor outcome with psychotherapy.[39] Replication of these findings could prove extremely helpful in guiding treatment.

Summary. It is premature to conclude that maintenance antidepressant treatment *per se* is either harmful or ineffective. It is also fallacious to infer from the Andrews et al study[24] that we ought to avoid or discontinue antidepressants in patients who have remained well for long periods while taking antidepressants. Current animal models suggest that acute antidepressant use may have *neuroprotective* effects against inflammation, oxidative stress, and ischemic injury,[41,34] and I am not aware of any animal models that show loss of neuroprotection or evidence of "oppositional tolerance" with chronic (1 month) antidepressant administration.[40] It may well be that antidepressants provide long-term neuroprotection in humans, but we simply do not know this; consequently, concerns regarding "oppositional tolerance" to antidepressants must be investigated further. Finally, although recent (unpublished) evidence[22] casts doubt on the claim that antidepressants provide genuine long-term, prophylaxis (past 6 months or so) in major depression, relapse prevention for six months is by no means a trivial benefit for severely and recurrently depressed persons.

QUESTION 3. Aren't antidepressants widely over-prescribed, often for inappropriate reasons?

Yes. There is good evidence that antidepressants are widely over-

prescribed to persons experiencing normal stress, sadness, or grief; who do not require treatment; or who have with mild depression and would be better off with psychotherapy.

No. Serious clinical depression is often overlooked or misdiagnosed, especially in primary care settings, and many patients with major depression are not receiving appropriate and adequate antidepressant medication.

Discussion. On the one hand, it is clear from several studies that antidepressant prescriptions in the United States are written much more frequently in recent years, and that only a small proportion of prescriptions are written by psychiatrists. For example, Mojtabai and Olfson[42] found that the rate of antidepressant drug treatment in the United States increased more than four times between early 1990s and early 2000s. Of special concern—and supporting the "Yes" position—Mojtabai and Olfson[42] found that the rate of antidepressant treatment increased more in the group of *less severely ill* individuals than in those with more severe psychopathology.

More recently, Mojtabai and Olfson (2011) have published a study[43] showing that, "Over the past two decades, the use of antidepressant medications has grown to the point that they are now the third most commonly prescribed class of medications in the United States. Much of this growth has been driven by a substantial increase in antidepressant prescriptions by nonpsychiatrist providers without an accompanying psychiatric diagnosis." Specifically, "the proportion of visits at which antidepressants were prescribed but no psychiatric diagnoses were noted increased from 59.5 percent to 72.7 percent."

These findings are certainly worrisome. On the other hand, the earlier Mojtabai and Olfson (2008) study[42] uncovered several socio-demographic disparities (e.g., racial/ethnic minorities continued to receive antidepressant treatment at a *lower rate* compared to non-Hispanic whites, raising concerns about *undertreatment* in some minority groups). This is consistent with the work of Gonzalez et al,[44] who found that Mexican American and African American individuals meeting 12-month major depression criteria consistently and significantly had lower odds for any depression therapy and guideline-concordant therapies.

Regarding the recent findings of increased antidepressant prescription by non-psychiatrists, it is important to highlight Mojtabai and Olfson's (2011)[43] own caveat: "These results do not clearly indicate a rise in inappropriate antidepressant use…" Rather, "…they highlight the need to gain a deeper understanding of the factors driving this national trend and to develop effective policy responses." These authors point to several such factors, including greater acceptance of antidepressants among the general public. It is also possible that some cases of antidepressant prescription by primary care physicians involve patients whose clinical picture does not meet full *DSM-IV* criteria for major depressive disorder, but may still represent a debilitating condition (e.g., the so-called "sub-threshold" depression, which is known to confer substantial distress and impairment).[45] Thus, the absence of a *DSM-IV* diagnosis, by itself, does not necessarily point to inappropriate treatment.

Also worrisome is a trend uncovered by Harman et al[46] of which the rates of *adequate* antidepressant treatment (e.g., using the minimum adequate daily dosage) peaked in 2002 (36.9%) and *declined significantly* by 2004 (31.7%) (p=0.003). The authors noted that this downward trend in adequate AD prescribing preceded the black-box warnings included on antidepressant labels beginning in 2004. There is also a large body of evidence showing that depression is under-recognized and under-treated in geriatric patient samples, often with inadequate dosing of antidepressants. Low rates of adequate depression care in elderly persons with chronic illnesses have also been reported.[47]

Synthesis. The notion that antidepressants are widely over-prescribed is clearly simplistic. There are undoubtedly "pockets" of over-prescription, perhaps mainly in primary care settings; but there are also *under-served* subgroups of depressed patients, often treated with sub-therapeutic antidepressant doses. Furthermore, to my knowledge, there are no well-designed, clinical studies showing that antidepressants are being widely or inappropriately prescribed for "ordinary grief" or uncomplicated bereavement, which, of course, would be inappropriate.[48]

The overall situation could best be summed up not as a crisis of treatment overkill, but of treatment *misalignment*. As Mojtabai and Olfson (2011)[43] put it:

"In general medical practice, antidepressant use appears to be becoming concentrated among people with less severe and poorly defined mental health conditions. Prescribing antidepressants without a psychiatric diagnosis is especially common in medical practices that prescribe the medications to a larger percentage of their patients. *Yet paradoxically, a large proportion of patients with common mental disorders do not receive needed treatment because their primary care providers do not detect their conditions. The widening misalignment between diagnosis and treatment suggests the need for a deeper inquiry.*"[43]

Indeed, the fundamental reality obscured by the debate over antidepressant prescribing is, as Hector Gonzalez, MD, put it, that "Few Americans with depression actually get any kind of care, and even fewer get care consistent with the [best practice] standards of care."[49,50] All this notwithstanding, my own recommendation is generally to reserve antidepressant use for cases in which A) *psychotherapy has failed to produce or maintain significant improvement, either acutely or prophylactically;* or B) *the clinical picture is one of*

pronounced suffering and incapacity, melancholic features,[8] *or high risk of suicide.* Long-term, maintenance treatment with antidepressants should be weighed carefully against the alternative of using some form of cognitive behavioral therapy (CBT). Nonetheless, in my view, the preferred treatment for most severely depressed patients will involve both pharmacotherapy and "talk therapy" of some kind.

CONCLUSION

Overall, it is fair to say that antidepressant treatment has been somewhat "oversold"—or at least over-marketed—in terms of its acute efficacy and demonstrable effectiveness in long-term prophylaxis. Nevertheless, there is compelling evidence that 1) for the *acute* treatment of *severe* depression, antidepressants are superior to placebo; and that (2) for severe *melancholic* depression, antidepressants are probably superior to both placebo and psychotherapy.[8] It is also likely that during at least the first six months after the index episode of MDD, and perhaps longer, antidepressants provide protection against relapse. However, it is not yet clear that they provide true, long-term, prophylactic protection. Moreover, there is concern that a subgroup of MDD patients may develop delayed ("oppositional") resistance and/or dysphoria with chronic antidepressant treatment use or have high recurrence rates if their antidepressants are discontinued. More study is needed to confirm these impressions and to determine the optimal rate of antidepressant tapering and discontinuation, both in maintenance studies and in clinical practice. *In my view, a much slower tapering period than usually employed—ideally, over 2 to 6 months—is worth exploring, both in clinical practice and as part of RCT research design.* This is consistent with the work of Baldessarini et al (2010)[51] who found that that, compared with gradual discontinuation, abrupt or rapid discontinuation of clinically effective antidepressant treatment was associated with a significantly shorter time to a first new episode of major depression.

For non-melancholic depressed patients, alternatives to long-term antidepressant treatment should be considered, including CBT and other forms of psychotherapy.[52] Finally, the issue of supposed "over-prescription" of antidepressants needs to be re-examined. It would be more accurate to say that there is a "mismatch" or misalignment of need with treatment, such that both over- and under-prescribing occur. Indeed, *inadequate antidepressant dosing* is a serious concern. Psychiatrists need to address these issues through both continuing medical education and public advocacy. Despite the ongoing controversy regarding the efficacy of antidepressants, a recent multicenter, observational study over a 27-year period suggests that antidepressant use is associated with a 20-percent reduction in the risk of suicide attempts or suicides—a finding that must give us pause in balancing the risks and benefits of these medications.[53]

Peter Abelard wisely observed that, "when…some of the writings of the saints seem not only to differ from, but even to contradict, each other, one should not rashly pass judgment…" (*Sic et Non*, preface). Neither should we jump to conclusions when our modern-day authorities on depression appear to reach divergent conclusions. Usually, there is some truth to be found on both sides of the issue.

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