Bipolar Disorders 2008: 10: 957–968

BIPOLAR DISORDERS

Review Article

Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression

Ghaemi SN. Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression.
Bipolar Disord 2008: 10: 957–968. © 2008 The Author Journal compilation © 2008 Blackwell Munksgaard

The widely held clinical view of 'antidepressants' as highly effective and specific for the treatment of all types of depressive disorders is exaggerated. This sobering conclusion is supported by recent findings from the NIMH-sponsored STEP-BD and STAR*D projects. Antidepressants have limited short-term efficacy in unipolar depressive disorders and less in acute bipolar depression; their long-term prophylactic effectiveness in recurrent unipolar major depression remains uncertain, and is doubtful in recurrent bipolar depression. These limitations may, in part, reflect the excessively broad concept of major depression as well as unrealistic expectations of universal efficacy of drugs considered 'antidepressants.' Treatment-refractory depression may reflect failure to distinguish depressive conditions, particularly bipolar disorder, that are inherently less responsive to antidepressants. Antidepressants probably should be avoided in bipolar depression, mixed manic-depressive states, and in neurotic depression. Expectations of antidepressants for specific types of patients with symptoms of depression or anxiety require critical re-evaluation. A revival of the concept of neurotic depression would make it possible to identify patients with mild-to-moderate, chronic or episodic dysthymia and anxiety who are unlikely to benefit greatly from antidepressants. Diagnostic criteria for a revival of the concept of neurotic depression are proposed.

S Nassir Ghaemi

Mood Disorders Program, Department of Psychiatry, Tufts Medical Center, Boston, MA, USA

Key words: antidepressants – bipolar depression – bipolar disorder – neurotic depression – STAR*D – STEP-BD – treatment resistant depression

Received 8 December 2007, revised and accepted for publication 6 June 2008

Corresponding author: S Nassir Ghaemi, MD, MPH, Mood Disorders Program, Department of Psychiatry, Tufts Medical Center, 800 Washington Street, #1007, Boston, MA 02111, USA.
Fax: 617 636 4852;
e-mail: nghaemi@tuftsmedicalcenter.org

> *If thought corrupts language, language can also corrupt thought.*
> George Orwell (1)

The term 'antidepressant' implies that such agents work for any kind of depression. This implication is enacted in the practice of clinicians as well as the belief systems of patients. The typical patient with depression who seeks help from a psychiatrist arrives with the assumption that the treatment for depression is an antidepressant. This would seem to be a simple matter of the English language.

SNG currently receives research grants from Pfizer and serves on the speakers bureau of AstraZeneca and Pfizer. Neither he nor his family holds equity positions in pharmaceutical corporations.

Hence, just as it is important to clarify what we mean by the term 'mood stabilizer' (2–4), it is necessary to define and describe what it means to say that a drug is an antidepressant.

What appears incorrect is the assumption that an antidepressant treats any kind of depressive condition.

What seems more correct, as this article will explain, is that an antidepressant is a drug with short-term, acute benefits in persons with a unipolar major depressive episode. By implication, antidepressants are not effective, or have little effect, in all other varieties of depressive conditions (e.g., bipolar depression, secondary depression, and 'neurotic depression').

Research on antidepressants has tended to have a standard design intended for Food and Drug

Administration (FDA) registration purposes, often an acute study of a single drug versus placebo. Important questions about long-term efficacy were infrequently asked, and head-to-head comparisons were uncommon, as were combination treatments. In the 1990s, partly to rectify this situation, the NIMH provided major one-time multicenter grants to study the three main severe mental illnesses [schizophrenia, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE); bipolar disorder, Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD); and unipolar depression, Systematic Treatment Alternatives to Relieve Depression (STAR*D)]. While these studies have their own limitations, these key projects provide new findings to assess clinical practice. This paper will provide a narrative review of this literature, seeking to identify where antidepressants are effective, and where they are not, in the spectrum of depressive disorders.

Bipolar depression

Acute studies

In bipolar depression, most studies have been conducted in the acute phase. A recent meta-analysis summarized this literature as of 2004 (5): only five double-blind, placebo-controlled studies had been conducted to that date. The meta-analysis excluded the only study (6) in which all patients received a proven mood stabilizer (lithium) on the grounds that the study reported remission rather than response data, and thus its results could not be pooled with other response data. Of the remaining studies, two involved selegiline [a monoamine oxidase inhibitor (MAOI) sometimes seen as being less effective than other MAOIs] alone versus placebo; one involved fluoxetine versus placebo (with lithium usage in about one-third of subjects; thus most patients received antidepressant monotherapy versus placebo alone, meaning no treatment); and the final study (which comprised about 75% of all subjects in the meta-analysis) involved fluoxetine + olanzapine versus olanzapine + placebo. Pooling these four studies, antidepressant was more effective than placebo; readers should note that placebo in some cases meant no specific drug treatment (although non-specific medical contact should not be undervalued), and in the largest study placebo meant olanzapine alone. In no case was an antidepressant + a proven mood stabilizer (like lithium) compared to a proven mood stabilizer alone. The plot gets more confusing when one examines the result of the only study with such a design, the one that was excluded, and there the antidepressant (either paroxetine or imipramine) was no better than placebo when added to lithium (6).

Beyond pointing out the inherent limitations of meta-analysis [some have likened it to 'statistical alchemy' (7)] when dealing with notable heterogeneity between study designs (8), these distinctions are relevant because they lead up to the recent STEP-BD study of acute bipolar depression (9) which, in my view, obviates the prior meta-analysis altogether. Excluding the olanzapine-fluoxetine study (n = 456), where the use of an antipsychotic as baseline medication makes the study less definitive, the STEP-BD is by far the largest study of antidepressants in acute bipolar depression [n = 366; the next largest study involved 117 patients (6)]. The STEP-BD study is also one of only two studies in which all patients are on baseline standard mood stabilizers (in the case of STEP-BD: lithium, divalproex, or carbamazepine). The result is that antidepressants are equal to placebo (with about 25% response in both categories). Further, antidepressants were equal to placebo in causing manic switch acutely (about 10% in both groups), which may reflect lower rates with the specific agents chosen partly for that purpose (bupropion and paroxetine), as well as the benefits of concomitant mood stabilizer treatment.

In summary, when added to standard mood stabilizers, antidepressants have been replicated, in the largest and best designed studies, as ineffective in acute bipolar depression. While the limited number of such studies, of course, make firm generalizations risky, our evidence base so far seems to best support these conclusions.

Maintenance studies

As of 2001, a systematic review demonstrated lack of benefit with antidepressants in maintenance treatment of bipolar disorder in randomized controlled trials (RCTs). Most of those studies involved imipramine [a tricyclic antidepressant (TCA)] added to or compared to lithium. In the past few years, two new maintenance RCTs have been conducted with antidepressants, mostly new generation agents. In one study conducted by the Stanley Network (10, 11), venlafaxine was compared to bupropion and sertraline in double-blind treatment, added to standard mood stabilizers, for up to one year. All three agents were similarly effective, with much more efficacy in the acute phase (about 50–60%, based on the standard definition of greater than 50% improvement in depression rating scales at two months) than in the maintenance phase (about 15–25%, based on prevention of relapse into a new

mood episode). In the absence of a placebo control, one cannot state whether there was any real efficacy in either phase, but numerically, it appears that whatever short-term benefit was seen diminishes greatly in longer-term treatment. In fact, as shown below, these figures are quite consistent with the findings of STAR*D in unipolar depression. It is also notable that the main finding of the Stanley study, besides low long-term efficacy, was elevated manic switch rates with venlafaxine compared to bupropion or sertraline (about 25% versus 10–12%), suggesting that manic switch can be seen, even with concomitant mood stabilizer treatment, with agents that may be more prone to induce it (perhaps noradrenergic agents like venlafaxine and TCAs are more prone than either purely serotonergic agents, or mildly dopaminergic agents).

The second maintenance study, as yet unpublished, was conducted by our group as part of the STEP-BD program (12). In that study, we recruited 70 subjects who had initially responded to a standard mood stabilizer (mostly lithium, carbamazepine, divalproex, or lamotrigine, although a minority were mainly treated with neuroleptics) plus an antidepressant [mostly serotonin reuptake inhibitors (SRIs) or bupropion]. These responders to antidepressants were then openly randomized to continue or discontinue their antidepressant two months after recovery from the acute major depressive episode. Mood stabilizers were continued in all patients, and follow-up was conducted for up to three years, with one year outcome being the primary cut-off. The primary outcome was improvement in overall mood morbidity using the Clinical Monitoring Form (CMF), a progress note DSM-IV criterion-based assessment of mood symptoms that was used in STEP-BD [shown to correlate well with standard mood rating scales (13)]. Overall mood morbidity reflected both manic and depressive symptoms; secondary outcomes assessed the two mood poles separately on their CMF scores, as well as overall time in remission (CMF scores at or near zero), and time to relapse into a first mood episode. A priori subgroup analyses were also planned to assess whether antidepressants worsened outcomes in those with rapid-cycling bipolar disorder, and improved outcomes in type II bipolar disorder. Data provided here are extensions of previous interim analyses (12) and full publication of data is occurring separately.

The results of our study can be divided into three parts: (i) where antidepressants produced benefit, (ii) where they did not, and (iii) where they produced harm. In the primary outcome, at one-year follow-up, simple analysis of mean differences found benefit from continuation of antidepressants for depressive morbidity, though with a modest effect size (about 1.5 mood episode criteria). Discontinuation of antidepressants did lead to more rapid relapse into a depressive episode. These were the benefits seen with antidepressants. However, they showed lack of benefit in a few other outcomes: overall, antidepressant continuation (versus discontinuation) did not lead to fewer mood episodes at one year, and when those mood episodes occurred, antidepressant continuation did not reduce their severity. Also, overall time in remission was not increased by antidepressant continuation, nor were better outcomes seen in type II bipolar disorder. Harm was seen in the rapid-cycling subgroup, where antidepressant continuation was statistically associated with more depressive episodes (about three times more than in non-rapid cyclers, in contrast to equal depressive morbidity stratified by rapid cycling in the antidepressant discontinuation group).

Overall, both new maintenance studies of new generation antidepressant medications, though limited by not having placebo controls, fail to find a robust effect size of benefit with antidepressants in bipolar disorder, though our study found some modest symptomatic benefit. This limited efficacy is consistent with at least five previous RCTs with TCAs. Further, our study confirmed the previous randomized data showing harmful effects of antidepressants in rapid cycling bipolar disorder (14).

Pure depression versus the depressive mixed state

These generally negative data might be seen as conflicting with benefits seen in recent studies with some antipsychotics and anticonvulsants in bipolar depression. The most obvious contrast is with two studies of quetiapine (15, 16), both of which were markedly better than placebo, which led to the only FDA indication for a single agent for acute bipolar depression. Similar efficacy has been shown with olanzapine-fluoxetine combination (OFC), though not with olanzapine alone, leading to FDA indication of OFC for acute bipolar depression (17).

One possible explanation for the relative inefficacy of antidepressants and the relative efficacy of antipsychotics in RCTs of acute bipolar depression might have to do with the distinction between the depressive mixed state and pure depression (18). The current DSM-IV definition of acute bipolar depression is quite broad, and that of the acute mixed episode correspondingly narrow (requiring that full mania criteria be met at the same time as full depression criteria). Patients can thus enter current acute bipolar depression studies with one, two, or

three manic symptoms (along with a major depressive episode), since that presentation is still below the high threshold set for the DSM-IV mixed episode. Some data indicate that up to one-half of subjects with bipolar depression have 1–3 manic symptoms (19), what has been termed the 'depressive mixed state' (18); the rates may be even higher in bipolar type II depression (20). Thus, studies of bipolar depression these days are likely to be studies of a mixture of the depressive mixed state and pure depression. This possibility remains a hypothesis until researchers examine bipolar depressed patients in RCTs more carefully for manic symptoms. It could be that such studies show benefit with antipsychotics because those agents may be especially effective in the depressive mixed state; similarly, such studies may show inefficacy with antidepressants because those agents may be especially ineffective in the depressive mixed state. The only study to assess that latter point was recently published from the STEP-BD database and it found no benefit with antidepressants in depressive mixed state subjects (21), which is consistent with the older literature on lack of benefit with antidepressants in mixed episodes in general.

Thus, perhaps this literature would be clarified if future antidepressant studies were conducted in only pure bipolar depressed subjects (excluding those with any manic symptoms), and if antipsychotic data were at least analyzed stratifying for presence or absence of any concomitant manic symptoms (analyses which have not yet been done with current studies). Future studies might even target antipsychotic treatment to the depressive mixed population.

One final comment on these antipsychotic studies: they demonstrate acute benefit, up to eight weeks, with agents like quetiapine. Thus, following the evidence to the letter would suggest that clinicians should use them for acute benefit, for eight weeks, but they do not provide a scientific basis for long-term maintenance treatment, on the order of years. These antipsychotic maintenance data do not compare or provide alternatives to, the completely different maintenance data that show long-term benefits with agents like lithium (22), divalproex (23), or lamotrigine (24); this distinction is reviewed in more detail elsewhere (25, 26). Simply put, lithium, divalproex and lamotrigine have all been shown to prevent depression with reasonably acceptable maintenance trial methodologies, while such depression prevention is not present with aripiprazole (27), is not clearly shown with olanzapine due to an acute discontinuation effect in its main placebo-controlled monotherapy trial (28), and only is shown with quetiapine as add-on treatment to standard mood stabilizers (not in monotherapy) (29). One study with olanzapine suggested similar depression prevention benefit versus lithium (30), but it was not placebo controlled. Thus, overall, while some maintenance benefit with neuroleptics may occur, especially as adjunctive treatments, the extent of their benefits is not robust or well replicated, especially for prevention of depressive episodes, and it is not at all established for some agents like ziprasidone or risperidone. The distinction between acute and maintenance efficacy needs to be maintained. It is not the case that acute efficacy translates into maintenance efficacy or vice versa (what might be called the 'happily ever after' fallacy).

Summary

In sum, the evidence indicates that antidepressants appear ineffective or quite limited in efficacy in acute or maintenance treatment of bipolar depression. They may be especially ineffective in the depressive mixed state. Their utility in pure bipolar depression has not been examined. Again, in the setting of a limited number of such studies, making firm generalizations is risky, but nonetheless these are reasonable interpretations, in my view, of the evidence base so far.

This evidence contrasts with the widespread usage of these agents in bipolar disorder [about 80% of patients receive antidepressants regardless of the country when comparing the US and Europe, a rate that is twice as high as any other class of agent, including mood stabilizers or antipsychotics (Adelphi Group Products, data on file, Cheshire, UK, 2003)]. One is left with a conundrum: either the studies are right and clinicians/patients are wrong; or the studies are wrong and clinicians/patients appreciate something that the studies have missed. Many are inclined to give clinicians the benefit of the doubt, but, in my view, the history of medicine would suggest otherwise, not only in the distant past (bleeding being the primary medical treatment for most illnesses from the 1st century AD until the 19th century), but recently (e.g., the extensive use of hormone replacement therapy was discouraged in many women by large RCTs; cigarettes were widely viewed as benign until large epidemiological studies showed their harm). Can tens of thousands of psychiatrists be wrong? History would suggest so.

Unipolar depression

Most of this discussion will relate to interpreting the results of the large NIMH-sponsored STAR*D

study, though some discussion of other studies will also be included.

Acute studies

In STAR*D, the main purpose was to see what antidepressant treatments were effective in those who failed to remit initially with a single antidepressant trial. The antidepressant chosen was citalopram, a typical SRI, and it was given open-label initially in order to identify non-responders, who were then randomized to various steps of other treatments. Perhaps not too surprisingly, initial response openly to citalopram was about 50%, and initial remission about 30% (31). The remaining subjects were then randomized to three sequential stages of treatment. They continued through the course of options if they failed to remit in any phase, and as long as they were willing to stay in the randomized studies. Figure 1 reflects the phases of treatments, as well as the acute and sustained response and remission rates.

As seen in Fig. 1, in the second stage of treatment (either switching to a different antidepressant or augmenting with one), a similar rate of acute response was achieved (about 50%). However, by stages 3 and 4, despite using agents previously shown to be most effective (like TCAs and MAOIs or lithium augmentation), acute response rates ranged around 20%. Further, by stages 2 and onward, remission and response rates were about the same (i.e., better response was not seen with a more liberal definition of improvement than used for remission). As the authors of STAR*D commented in one paper, one can read these results as good news in the sense that one can conclude, with multiple phases of treatment, that about 60% or so of patients will respond acutely (>50% improvement in depressive symptoms) (32). When one incorporates dropouts due to side effects, as I did in the figure, that acute response rate seems to fall to about 51%, but still one-half of patients seem to benefit. Again, the absence of a placebo control obviates definitive conclusions, but in the context of the extensive non-STAR*D literature on this topic, one might be justified in concluding that antidepressants have acute benefit in about one-half of people with unipolar depression.

Maintenance studies

Though STAR*D is mainly reported in terms of its acute data, one analysis so far also provides

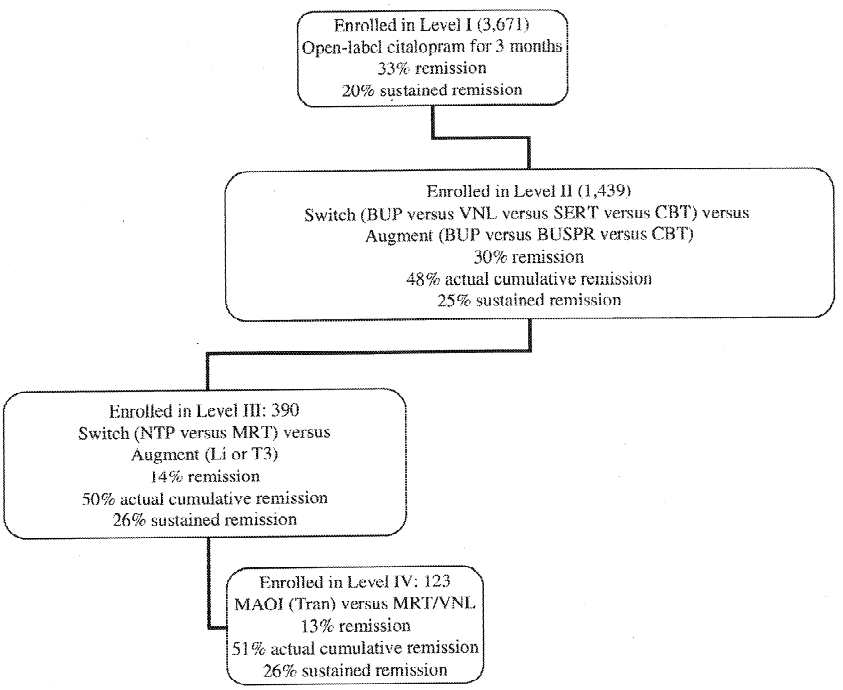

Fig. 1. STAR*D cumulative response and remission rates. Rate (%) estimates are based on reanalysis of data from Rush et al. (32). BUP = bupropion; VNL = venlafaxine; SERT = sertraline; CBT = cognitive behavioral therapy; BUSPR = buspirone; NTP = nortriptyline; MRT = mirtazapine; Li = lithium carbonate; T3 = tri-iodothyronine; MAOI = monoamine oxidase inhibitor.

maintenance data (32), and it is perhaps underappreciated that the STAR*D maintenance data may be the best evidence that we have to date on long-term efficacy with antidepressants in unipolar depression. Further, STAR*D was designed to be, and is, generalizable to the real world of complex, comorbid, recurrently depressed patients, as opposed to the cleaner populations studied in most RCTs (designed for FDA registration by the pharmaceutical industry).

The basic results are as follows (see Fig. 1): of the subjects who acutely responded or remitted to antidepressants in STAR*D, only about one-half stayed well at one year (sustained remission). In other words, by preselecting those patients who have acute benefit with antidepressants, as noted above, one-half will maintain benefit. Since one-half receive acute benefit, and one-half of that group have sustained maintenance benefit, only one-quarter of the overall sample has long-term maintenance remission with antidepressants in unipolar depression, according to STAR*D. Remission and the more liberal criterion of response seemed to converge by the end of STAR*D, so that this 25% long-term improvement rate should not necessarily mean that another chunk of patients (approximately another 25%) did not have remission but might have had partial improvement. The published data so far suggest that a 25% benefit is about all there is with long-term treatment, however we define such benefit. If other data are available on this topic in the STAR*D database, they should be analyzed. Otherwise, we would have to conclude that there is much less long-term benefit with antidepressants in unipolar depression than has often been assumed and, further, that this benefit is in fact rather similar to the long-term efficacy seen in bipolar depression [also around 20% in the recent Stanley Network RCT (10)]. These results then might argue that antidepressants are not equally effective in bipolar and unipolar depression (33), nor differentially effective in unipolar as opposed to bipolar depression (34), but equally ineffective in both conditions. Yet this latter pessimistic conclusion is not entirely accurate: it would apply to low long-term maintenance benefits, keeping in mind higher amounts of acute benefits in unipolar depression as seen in STAR*D, in contrast to limited or no acute efficacy with antidepressants in bipolar depression in STEP-BD.

If one asks how these STAR*D studies compare to other maintenance studies of antidepressants in unipolar depression, it is important to note that the rest of the literature is sponsored by the pharmaceutical industry, which tends to avoid publishing negative studies. A recent review of mostly acute antidepressant trials found that the published literature was 94% positive, but when unpublished negative studies are included, the actual study database is 51% positive (35). This problem of publication bias is thus endemic to any meta-analysis limited to the published literature, as with one on long-term antidepressant trials (36). In that report, 10 studies with SRIs (n = 2,080) and 15 with TCAs (n = 881), mostly with one year follow-up, showed maintenance benefit versus placebo. The longest follow-up with modern antidepressants was two years with venlafaxine (37).

The benefit of these studies is that they have pure placebo controls, unlike STAR*D. However, the magnitude of benefit seen in these studies, often masked in published reports, is not better than the low rate of improvement seen in STAR*D. For instance, in a recent venlafaxine maintenance study (37, 38) 1,096 patients initially entered an acute depression study and were randomized to venlafaxine versus fluoxetine. A total of 715 responders were then enrolled in six-month blind continuation on the same treatment. A total of 258 responders at six months entered maintenance phase A for one-year treatment (re-randomized to venlafaxine versus placebo) and 131 responders (83 venlafaxine, 48 placebo) in maintenance phase A entered phase B for a second year of maintenance (venlafaxine responders were re-randomized to venlafaxine versus placebo while placebo responders stayed on placebo, and fluoxetine responders stayed on fluoxetine). In the first year of maintenance treatment (phase A) in 258 responders, 77% stayed well on venlafaxine versus 58% with placebo. In the second year of maintenance treatment, the venlafaxine response rate was 92% (of those who respond at one year) versus only 20% with placebo. These response rates seem quite large, especially when compared to STAR*D, but only because these percentages are being reported in smaller and smaller subgroups.

Here are the response rates from the start of this study: (i) of the original sample (n = 1,096) 65.2% had an acute response; (ii) 35.9% (258/715) of those acute responders remained well at six months; (iii) 50.8% (131/258) of sustained responders at six months remained well at 18 months. This is only 18.3% (131/715) of initial sustained responders at one year. The massive 92% response rate at two years only applies to this subgroup (18.3% of the original sample). Thus, the grand total of responders at two years is 92% of 18.3%, which is 16.8% of original sustained responders (at six months).

This low absolute response rate is in the range of the low sustained response/remission seen in STAR*D. Though it is not unique to antidepressant maintenance studies [similar calculations could be made with lamotrigine or aripiprazole maintenance data in bipolar disorder (27, 39)], it is relevant that efficacy greater than placebo does not mean efficacy in most persons. The actual effect size of long-term absolute benefit is small. It is also the case that dropouts in long-term clinical trials is a complex matter, including the difficulty of maintaining patients in randomized studies, but the general point that is relevant is that relative percentage response rates (such as 92% at two years) are also inflated, and some attention should be paid to the absolute number of patients who remain in these studies.

Treatment refractory depression (TRD)

The main purpose of STAR*D was to identify treatments for refractory depression. But perhaps its most obvious finding is that after two initial trials (where about 50% acute response rates are seen), further antidepressant treatments or combinations have much lower rates of response (in the 10–25% range), and cumulative sustained remission after two treatment trials is quite small, especially when recovery based on natural history is also taken into account.

The TRD literature, which has for so long recommended multiple trials of antidepressants in various combinations, would thus seem to be overoptimistic. This observation may be supported by recent studies which suggest that TRD is not really simply a case of unipolar depression that happens not to respond well to antidepressants. Of the many causes often cited as risk factors for TRD (such as misdiagnosis, comorbid personality disorders, medical illnesses, substance abuse, rapid metabolism, etc.) (40), few TRD studies in the past have tried to quantify the frequency of these risk factors. Recent data suggest that perhaps, of that long list, the others pale in comparison to a major cause: misdiagnosis (41). In patients diagnosed with refractory unipolar depression and unresponsive to multiple therapeutic antidepressant trials, upon careful diagnostic reassessment, two studies indicate that about 25–50% instead have bipolar depression (most commonly type II) (42, 43). (It is not claimed here that this was the case with STAR*D, which systematically assessed and excluded types I and II bipolar disorder; but these studies suggest this misdiagnosis is an important factor in TRD in real-world practice).

Galen once remarked, 'My treatment fails only in incurable cases' (44). The concept of TRD is similar; rather than doubting our clinical concepts, we blame the illness. Instead, it appears that the main problem of TRD may not be so much that our antidepressants are not working enough, but rather that we are getting the diagnosis wrong.

Neurotic depression

Most patients treated with antidepressants do not have either bipolar depression, or recurrent unipolar depression, or mixed states, or TRD. Most have mild to moderate chronic depressive and anxiety symptoms that impair their lives, but which do not usually meet major depressive episode criteria. In fact, these persons probably see primary care physicians (who prescribe antidepressants more than psychiatrists) as frequently as psychiatrists. It is likely that antidepressant use fails to provide major benefits in this population, partly because the best diagnosis for this group of patients was legislated out of existence with DSM-III in 1980, and in its later revisions. In initial drafts, the DSM-III committee required criteria for major depressive disorder and bipolar disorder, but removed reference to what had been termed 'neurotic depression.' This decision appears to have been based in part on frankly speculative, mechanistic, psychoanalytic connotations associated with the term, including the hypothesis that unconscious intrapsychic conflicts can *cause* depressive and associated anxiety symptoms (45). A backlash arose from many clinicians, including many with psychodynamic training. A compromise was reached by including new diagnostic categories of *generalized anxiety disorder* and *dysthymia*, in large part so as to capture patients formerly considered to have neurotic depression. Neurotic depression was renamed, but its treatment was not. As antidepressants came to be used increasingly for 'major depression,' clinicians simply reconceived of formerly neurotic depressed patients as simply 'depressed,' possibly considered to meet criteria for a major depressive episode at some times. Yet anxiety is often equally if not more prominent in this syndrome, and episodicity often is not characteristic of such patients. In practice, the diagnoses of major depression, dysthymia, and generalized anxiety are often melded together, or anxiety symptoms are considered as 'comorbidities' to major depression or dysthymia (46). A principal outcome of the imprecise distinction among the various groups of patients with

depressive morbidity was to treat them all with 'antidepressants'.

However, neurotic and major depression patients are very different in their diagnostic validators (47) of phenomenology, genetics, course, and treatment response, and both are different from the depressive phases of bipolar disorders. Typically, neurotic depression patients have less severe depression and more prominent anxiety symptoms, as well as a high degree of sensitivity to psychosocial stressors, than is usual in recurrent major depressive disorder, and they are likely to follow a chronic, and not episodic, course (48). Moreover, twin studies indicate separate heritability for chronic depressive-anxiety disorders versus major depressive disorder (49). It would also not be surprising if neurotic and major depressive disorders also differed in treatment response. This hypothesis remains poorly studied, partly because the term 'neurotic depression' has fallen out of use. Nevertheless, some (50, 51), though not all (52), evidence suggests that patients with chronic depression generally are less responsive than those with briefer episodes of major depression, as are those with anxiety (53, 54), dysthymia (54, 55), or mild depressive symptoms (56). These tentative conclusions do not imply that antidepressants are completely ineffective in dysthymia or generalized anxiety disorder (57, 58), but they may be less effective in these chronic settings than otherwise.

More than a decade ago, Martin Roth warned about the changes in DSM-III that included deletion of neurotic depression as a diagnosis (59). Based on data then available, he made a good case that some patients with depressive symptoms could be distinguished from recurrent unipolar major depressive disorder. Subsequent research appears to have confirmed Roth's views. In Table 1, a proposal is made for diagnostic criteria for neurotic depression which incorporate DSM-IV definitions for generalized anxiety disorder, dysthymia, and major depressive disorder, and distinguish neurotic depression from recurrent unipolar major depressive disorder.

In part, antidepressants may have yielded disappointing long-term results in the STAR*D study because the DSM-IV diagnostic category of 'major depressive disorder' is too broad. The major depression concept ranges from single depressive episodes of widely ranging severity and clinical characteristics (including melancholic and psychotic forms, with a wide range of onset-ages), through patients with only a few recurrences, to highly recurrent major depressive episodes of varying duration clearly separated from periods of apparent euthymia (60). As employed clinically, the diagnosis includes chronic depression with a range of clinical features, severity and duration, as well as many cases of neurotic depression. It is tempting to speculate that both episodicity and chronicity of depressive symptoms associate with inferior responses to antidepressants.

Table 1. Proposed diagnostic criteria for neurotic depression[a]

A. The presence of depressed mood more intense or disabling than, but not distinct from, normal sadness
B. At least 2 but not more than 4 of the following criteria are met: sleep changes (decreased or increased), decreased interest in usual activities, low self-esteem, decreased energy, decreased concentration, appetite changes (decreased or increased), suicidal ideation
C. Chronic worries or psychological anxiety most of the day, nearly every day, OR multiple somatic symptoms, such as gastrointestinal distress (e.g., nausea, diarrhea), headaches, or paresthesia
D. Duration of symptoms in criteria A, B, and C is at least six months, lasting most of the day, nearly every day
E. Mood appropriately reactive to adverse or favorable changes in life circumstance and to everyday events
F. Absence of marked psychomotor retardation or marked guilt/self-reproach
G. DSM-IV major depressive episode criteria are not met during most of the duration of the above symptoms
H. DSM-IV criteria for major depressive episode, chronic subtype, are not met

[a]Adapted from Schapira et al. (55).

'Episodicity', as Goodwin and Jamison (61) have emphasized, has been linked with bipolar disorder, and indeed was included in the original Kraepelinian concept of manic-depressive illness. What mattered was that patients had many mood episodes of whatever variety (even all depressive) (61). Of note, there is evidence that 'highly recurrent' (still ill defined) unipolar depression is potentially responsive to lithium (62). 'Chronicity,' as Roth emphasized, also may associate with a different condition, and it may well be less antidepressant-responsive than episodes of acute major depression.

About one-third of persons diagnosed with unipolar major depressive disorder have one or a few episodes, but not a highly recurrent or chronic course (61). Antidepressants may be more effective in a targeted population involving major depressive episodes that are not highly recurrent or chronic, than in the broader mix of patients currently diagnosed with imprecisely defined 'depressive disorders'.

In this discussion, the natural history of untreated outcomes is important, and can be ascertained among patients before treatment, or during prolonged periods without treatment. Most research on the course of depressive disorders precedes the definition and broad

acceptance of antidepressant drugs in the 1970s and later (45). Recent studies find notable rates of chronic subsyndromal or dysthymic depression in bipolar disorder (63). Perhaps importantly, these observations arise in treated patient cohorts, and thus do not represent natural history. These findings represent the results of treatment with mood stabilizers, antipsychotics, and sedatives that effectively suppress manic features in bipolar disorder. In contrast, the natural history of untreated bipolar disorder is primarily episodic, not chronic (61).

Advice for clinical practice

The main point of this essay is that a rethinking of the use of antidepressants is needed. This recommendation is not merely an academic or scientific matter, but also addresses a practical clinical problem. Clinicians would do well to return to, and better appreciate, the classic Hippocratic tradition in medicine, not merely as words to be mouthed, but rather as a living source of guidance about how to ethically and scientifically practice medicine in the setting of uncertainty.

The Hippocratic tradition helps clarify our clinical obligations. The job of the physician in that tradition is not to meet every symptom with a pill. If this allopathic practice were the case, then the first two years of medical school, entirely devoted to understanding diseases, would probably be unnecessary. The physician needs to determine if the patient's presenting signs and symptoms add up to a disease, and if so, then whether and how that disease has been demonstrated to be best treated. If the patient has no disease, then treatments should be avoided, or if given, used short term for an explicitly palliative purpose. Such Hippocratic practice is rarely followed in contemporary psychiatric pharmacotherapy (64).

One should not conclude that the limited benefits provided by antidepressants 'are better than nothing.' Such a view would reflect the extent to which contemporary psychiatry has become non-Hippocratic, and would be based on the dour assumption that we should treat until our treatments are proven ineffective. The Hippocratic tradition argues the reverse: patients should not receive a treatment until it is proved to yield better outcomes than the natural history of the illness. In other words, the burden of proof in contemporary psychiatric therapeutics appears to require reasons to *avoid* using medications, whereas the Hippocratic tradition requires a burden of proof to *use* them (64).

The other practical conclusion from this article is that we need to get our metaphors right. Until now, an analogy of major depressive disorder to chronic illnesses, such as diabetes mellitus, has been widely assumed: antidepressants, like insulin, are needed for long-term management. Perhaps we should shift the analogy to infectious diseases: antidepressants for depressive disorders might be analogized to antibiotics: effective, sometimes essential and even life-saving, in acute illness, but ineffective or dangerous in excessive or overly prolonged use.

If this interpretation of the Hippocratic tradition is correct, and if the new analogy to antibiotics is valid, then the job of the practicing clinician comes down to two steps. First, more careful and precise diagnosis is needed. Since nosology precedes pharmacology, if we get the diagnosis wrong, treatment will be ineffective. For example, bipolar depression should be recognized or suspected far more often, and antidepressants generally avoided in such cases. Moreover, 'major depressive disorder' needs to be considered in its clinically important subtypes. Recurrent, episodic unipolar depressive episodes could be treated short term with antidepressants, and then continued only when relapse occurs, or when recurrences are frequent. First-episode unipolar, major depression patients should receive short-term antidepressant treatment. Chronic neurotic depression could be treated with antidepressants for perhaps several months, and continued only if relapses occur, ideally with psychotherapy as well.

Suggestions for future research

This critique is not meant to be an exercise in nay-saying. The point of this discussion is not to dismiss antidepressants in psychiatry, with nothing more to say. Rather, science proceeds with critique of current knowledge, followed by experiment, to try to establish new knowledge. Truth is the goal at which this gradual process of corrected error aims. Among suggested lines for future research, the following may be relevant:

First, nosologic research should be conducted on patients who meet a construct for neurotic depression. In Table 1, suggested diagnostic criteria are provided, adapted from the work of Roth's group over three decades ago (55). To validate this concept of neurotic depression, these criteria can be examined in studies comparing unipolar depression populations in symptom prevalence, family

history, course of illness, and antidepressant treatment response.

Second, the efficacy of psychotherapies versus no treatment versus antidepressants is important to study in this proposed neurotic depression population.

Third, antidepressant discontinuation studies are needed that compare long-term outcomes in patients who respond acutely to antidepressants.

Fourth, such long-term maintenance studies should also ideally include a psychotherapy comparison group to determine if maintenance-phase psychotherapy is effective versus long-term antidepressant treatment.

Fifth, all such studies should be analyzed not only with DSM-IV major depressive disorder definitions, but also looking at subgroup efficacy in non-recurrent episodic unipolar depression (one or two episodes), recurrent episodic unipolar depression (three or more episodes), chronic major depression (DSM-IV defined as major depressive episodes lasting longer than one year), neurotic depression (see Table 1), and bipolar spectrum disorder [recurrent depressive episodes with features of bipolarity other than spontaneous manic or hypomanic episodes (65)].

Lastly, specific psychotherapies can be examined, such as cognitive behavioral therapy (CBT), but more attention should also be given to effects of the most common kind of psychotherapy, a nonspecific eclectic mix of mostly psychoanalytic techniques with supportive and behavioral methods, which is highly understudied (66). A final kind of psychotherapy that is little studied and may have particular benefit in depressive conditions is existential psychotherapy (67), which, despite its apparently subjective nature, is amenable to empirical assessment of outcomes (68).

References

1. Orwell G. Politics and the English language. Essays. London: Penguin, 2000.
2. Ghaemi SN. On defining 'mood stabilizer'. Bipolar Disord 2001; 3: 154–158.
3. Bauer MS, Mitchner L. What is a "mood stabilizer"? An evidence-based response. Am J Psychiatry 2004; 161: 3–18.
4. Goodwin GM, Malhi GS. What is a mood stabilizer? Psychol Med 2007; 37: 609–614.
5. Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004; 161: 1537–1547.
6. Nemeroff CB, Evans DL, Gyulai L et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001; 158: 906–912.
7. Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. J Clin Epidemiol 1995; 48: 71–79.
8. Eysenck HJ. Meta-analysis and its problems. BMJ 1994; 309: 789–792.
9. Sachs GS, Nierenberg AA, Calabrese JR et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007; 356: 1711–1722.
10. Post RM, Altshuler LL, Leverich GS et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 2006; 189: 124–131.
11. Leverich GS, Altshuler LL, Frye MA et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006; 163: 232–239.
12. Ghaemi SN, El-Mallakh RS, Baldassano CF et al. A randomized clinical trial of efficacy and safety of long-term antidepressant use in bipolar disorder (abstract). Bipolar Disord 2005; 7(Suppl. 2): 59.
13. Sachs GS, Guille C, McMurrich SL. A clinical monitoring form for mood disorders. Bipolar Disord 2002; 4: 323–327.
14. Wehr TA, Sack DA, Rosenthal NE, Cowdry RW. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. Am J Psychiatry 1988; 145: 179–184.
15. Calabrese JR, Keck PE Jr, Macfadden W et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005; 162: 1351–1360.
16. Thase ME, Macfadden W, Weisler RH et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol 2006; 26: 600–609.
17. Tohen M, Vieta E, Calabrese J et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003; 60: 1079–1088.
18. Koukopoulos A, Albert MJ, Sani G, Koukopoulos AE, Girardi P. Mixed depressive states: nosologic and therapeutic issues. Int Rev Psychiatry 2005; 17: 21–37.
19. Benazzi F. Bipolar disorder – focus on bipolar II disorder and mixed depression. Lancet 2007; 369: 935–945.
20. Benazzi F. The clinical picture of bipolar II outpatient depression in private practice. Psychopathology 2001; 34: 81–84.
21. Goldberg JF, Perlis RH, Ghaemi SN et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. Am J Psychiatry 2007; 164: 1348–1355.
22. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004; 161: 217–222.
23. Gyulai L, Bowden C, McElroy S et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 2003; 28: 1374–1382.
24. Goodwin GM, Bowden CL, Calabrese JR et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 2004; 65: 432–441.
25. Ghaemi SN. Mood Disorders: A Practical Guide, 2nd edn. Philadelphia: Lippincott, Williams, and Wilkins, 2007.

26. Ghaemi SN, Pardo TB, Hsu DJ. Strategies for preventing the recurrence of bipolar disorder. J Clin Psychiatry 2004; 65(Suppl 10): 16–23.
27. Keck PE Jr, Calabrese JR, McIntyre RS et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 2007; 68: 1480–1491.
28. Tohen M, Calabrese JR, Sachs GS et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 2006; 163: 247–256.
29. Brecher M, Anderssen H, Paulsson B. Quetiapine in the maintenance treatment of bipolar I disorder: combined data from two long-term phase III studies (abstract). Bipolar Disord 2008; 10(Suppl. 1): 40.
30. Tohen M, Greil W, Calabrese JR et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005; 162: 1281–1290.
31. Trivedi MH, Rush AJ, Wisniewski SR et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163: 28–40.
32. Rush AJ, Trivedi MH, Wisniewski SR et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163: 1905–1917.
33. Grunze H. Reevaluating therapies for bipolar depression. J Clin Psychiatry 2005; 66(Suppl 5): 17–25.
34. Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ. Antidepressant treatment in bipolar versus unipolar depression. Am J Psychiatry 2004; 161: 163–165.
35. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008; 358: 252–260.
36. Geddes JR, Carney SM, Davies C et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003; 361: 653–661.
37. Keller MB, Trivedi MH, Thase ME et al. The prevention of recurrent episodes of depression with venlafaxine for two years (PREVENT) study: outcomes from the 2-year and combined maintenance phases. J Clin Psychiatry 2007; 68: 1246–1256.
38. Kocsis JH, Thase ME, Trivedi MH et al. Prevention of recurrent episodes of depression with venlafaxine ER in a 1-year maintenance phase from the PREVENT Study. J Clin Psychiatry 2007; 68: 1014–1023.
39. Calabrese J, Bowden C, Sachs G et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003; 64: 1013–1024.
40. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. Can J Psychiatry 2007; 52: 46–54.
41. Malhi GS, Parker GB, Crawford J, Wilhelm K, Mitchell PB. Treatment-resistant depression: resistant to definition? Acta Psychiatr Scand 2005; 112: 302–309.
42. Sharma V, Khan M, Smith A. A closer look at treatment resistant depression: is it due to a bipolar diathesis? J Affect Disord 2005; 84: 251–257.
43. Inoue T, Nakagawa S, Kitaichi Y et al. Long-term outcome of antidepressant-refractory depression: the relevance of unrecognized bipolarity. J Affect Disord 2006; 95: 61–67.
44. Jouanna J. Hippocrates. Baltimore, MD: Johns Hopkins University Press, 1999.
45. Healy D. The Antidepressant Era. Cambridge, MA: Harvard University Press, 1998.
46. van Praag HM. Comorbidity (psycho) analysed. Br J Psychiatry Suppl 1996; 30: 129–134.
47. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970; 126: 983–987.
48. Rodriguez BF, Bruce SE, Pagano ME, Keller MB. Relationships among psychosocial functioning, diagnostic comorbidity, and the recurrence of generalized anxiety disorder, panic disorder, and major depression. J Anxiety Disord 2005; 19: 752–766.
49. Kendler KS, Neale MC, Kessler RC. Major depression and generalized anxiety disorder: same genes, (partly) different environment? Arch Gen Psychiatry 1992; 49: 16–722.
50. Fawcett J. Antidepressants: partial response in chronic depression. Br J Psychiatry Suppl 1994; 26: 37–41.
51. Simon GE. Long-term prognosis of depression in primary care. Bull World Health Organ 2000; 78: 439–445.
52. Viguera AC, Baldessarini RJ, Friedberg J. Discontinuing antidepressant treatment in major depression. Harv Rev Psychiatry 1998; 5: 293–306.
53. Silverstone PH, von Studnitz E. Defining anxious depression: going beyond comorbidity. Can J Psychiatry 2003; 48: 675–680.
54. Hermens ML, van Hout HP, Terluin B et al. The prognosis of minor depression in the general population: a systematic review. Gen Hosp Psychiatry 2004; 26: 453–462.
55. Schapira K, Roth M, Kerr TA, Gurney C. The prognosis of affective disorders: the differentiation of anxiety states from depressive illnesses. Br J Psychiatry 1972; 121: 175–181.
56. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the food and drug Administration. PLoS Med 2008; 5: e45.
57. Thase ME, Fava M, Halbreich U et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. Arch Gen Psychiatry 1996; 53: 777–784.
58. Keller MB, McCullough JP, Klein DN et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000; 342: 1462–1470.
59. Roth M, Kerr T. The concept of neurotic depression: a plea for reinstatement. In: Pichot P, Rein W eds. The Clinical Approach in Psychiatry. Paris, France: Synthelabo, 1994.
60. Angst J, Merikangas K, Scheidegger P, Wicki W. Recurrent brief depression: a new subtype of affective disorder. J Affect Disord 1990; 19: 87–98.
61. Goodwin F, Jamison K Manic Depressive Illness, 2nd edn. New York: Oxford University Press, 2007.
62. Coppen A, Abou-Saleh MT. Lithium in the prophylaxis of unipolar depression: a review. J R Soc Med 1983; 76: 297–301.
63. Judd LL, Akiskal HS, Schettler PJ et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002; 59: 530–537.
64. Ghaemi SN. Toward a hippocratic psychopharmacology. Can J Psychiatry 2008; 53: 189–196.

65. Ghaemi SN, Ko JY, Goodwin FK. "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. Can J Psychiatry 2002; 47: 125–134.
66. Dewan MJ, Huszonek J, Koss M, Hardoby W, Ispahani A. The use of antidepressants in the elderly: 1986 and 1989. J Geriatr Psychiatry Neurol 1992; 5: 40–44.
67. Ghaemi SN. Feeling and time: the phenomenology of mood disorders, depressive realism, and existential psychotherapy. Schizophr Bull 2007; 33: 122–130.
68. Goldner-Vukov M, Moore LJ, Cupina D. Bipolar disorder: from psychoeducational to existential group therapy. Australas Psychiatry 2007; 15: 30–34.