

Hippocrates and Prozac: The Controversy About Antidepressants in Bipolar Disorder

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ABSTRACT

The controversy surrounding use of antidepressants in bipolar disorder is unlikely to be resolved by "evidence" because of the major influence of popular belief about psychopharmacology. This article suggests that among the relevant beliefs is a feeling among many Americans that favors being active and highly energetic, and an economic drive for a pharmacologic means of achieving that state of well-being and productivity. Further, this article suggests that psychiatrists have lapsed into a largely unscientific practice of psychopharmacology, often unaffected by evidence and driven by a symptom-based orientation to treatment. This approach to psychopharmacology breaks the maxims of the Hippocratic tradition of medicine, not simply on ethical grounds, but also due to a lack of understanding of the relevance of the nature of disease and the role of the doctor in relation to nature in the healing process. Further, basic standards of scientific methodology are often not well understood by clinicians and psychiatric researchers alike. Overall, a scientifically sound assessment of the evidence regarding the use of antidepressants in bipolar disorder, combined with a Hippocratic approach to psychopharmacology, supports more caution in the use of antidepressants for bipolar disorder.

Needs Assessment: Clinicians extensively use antidepressants for bipolar disorder but are often unaware of the limited research on this topic, most of which suggests lack of efficacy of those agents and notable risks of harm. Awareness of this research is important to improve clinical practice. Further, clinical psychopharmacology is often symptom-oriented and does not take into account the natural history of bipolar disorder. More understanding of a diagnosis-based approach to psychopharmacology of bipolar disorder, informed by an understanding of its natural history, is needed.

Learning Objectives:

- Examine the randomized literature on acute and maintenance efficacy of antidepressants in bipolar depression.
- Recognize Hippocratic methods to treatment in medicine, as applied to psychopharmacology of mood disorders.

Target Audience: Primary care physicians and psychiatrists.

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INTRODUCTION

"If you can't comfort the afflicted, you can at least afflict the comfortable."¹ —John Kenneth Galbraith

Depression in bipolar disorder is dangerous and difficult. Yet perhaps more dangerous is the psychiatric profession's lack of attention to it and a certain blithe belief in cure with antidepressants. For decades, most psychiatrists have practiced, and continue to do so, as if antidepressant use in bipolar disorder was uncontroversial. In recent years, a controversy has begun, as this assumption has been thrown into doubt based on research and clinical experience. This article outlines this controversy and places it in the context of psychiatric practice and research. Analyses published elsewhere by the author will not be repeated, but rather general conclusions of those analyses will be described. Readers are referred to those articles for more detail.²⁻⁴

THE AGE OF INNOCENCE

There was a time when antidepressants were unknown and depression was not diagnosed. This is not to say that depressed patients were not seen by psychiatrists; rather, they were diagnosed with manic-depressive illness, and, in the hands of caring physicians, given "moral therapy" and its varieties.⁵ (In the hands of more aggressive doctors, they would have received colectomies, lobotomies, or malaria therapy.⁶) As discussed by Saggese and colleagues⁷ in this issue, Emil Kraepelin held a view of manic-depressive illness that did not separate mania from depression. Rather, all recurrent mood episodes were viewed as one illness.⁸

In the 1960s, genetic and course studies⁹ began to suggest that perhaps polarity could distinguish two types of mood disorders, namely, bipolar and unipolar. The rise of lithium, phenothiazines, and tricyclic antidepressants (TCAs) seemed to provide practical relevance to the distinction (lithium and phenothiazines being effective in mania but not depression, and vice versa for TCAs). This trend of thinking led to the bipolar/unipolar dichotomy occurring in 1980 in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (*DSM-III*).¹⁰ Bipolar disorder was now narrowly defined; a full acute mania marked the diagnosis. Everything else was considered unipolar depression, which was a broad heterogeneous diagnosis.

Not surprisingly, the 1980s saw a rapid rise in unipolar depression diagnosis. In 1988, fluoxetine inaugurated in the United States a new generation of antidepressants that were not toxic in overdose and were otherwise well-tolerated. Again, not surprisingly, an antidepressant boom ensued.

LOVING ANTIDEPRESSANTS, HATING ANTIDEPRESSANTS

Emblematic of this antidepressant boom are two books which reflect the ambivalence of society to this process. In 1991, soon after President George Bush christened those years as "The Decade of the Brain," Peter D. Kramer, MD, published the best-selling *Listening to Prozac*,¹¹ a series of case vignettes of people whose lives had been transformed by the new antidepressant fluoxetine. It was not just that their depression had gone away; most had been only moderately depressed. Rather, these patients were able, within months of starting the medication, to achieve transformations of their personality. They encountered major changes in psyche and behavior which used to be thought of as the province of years of hard-fought psychoanalytic psychotherapy. Kramer saw fluoxetine as a unique psychotherapy in a pill with the promise of enhancing personality traits and not simply treating disease.

Kramer was not unaware of the ethical and philosophical issues implied by these observations. Yet, his overall affirmative stance toward the new antidepressants contrasted with the devastating critique published a few years later by British psychiatrist David Healy, MD, FRCPsych, in *The Antidepressant Era*.¹² Healy showed how the pharmaceutical industry had been instrumental in not only developing antidepressants but in influencing the profession of psychiatry regarding how to diagnose or conceptualize depression. While Kramer suggested that antidepressants may have a role outside of traditional disease definitions, Healy was throwing those traditional disease concepts into doubt, at least in the way they had evolved in contemporary psychiatry.

THE PURSUIT OF HAPPINESS

The American public has an ambivalence about antidepressants. On the one hand, clinicians have the daily experience of patients seeking treatment with antidepressants. Millions take them and for most of the 1990s, antidepressants were highly represented among the most frequently prescribed medications for any kind of medical condition. Billions of dollars in annual revenue were generated, providing profit margins in the pharmaceutical industry that dwarfed most other sectors of the economy.¹³ On the other hand, many Americans refused to take antidepressants or became noncompliant with the medications after beginning them. Antipsychiatry groups, such as the Church of Scientology, led protests and public campaigns against antidepressant use, especially in children. Lawsuits alleging harm from antidepressants, including violence and suicide, occurred. This backlash increased after the Food and Drug Administration indeed found a small absolute

but notable relative risk of suicidal behavior in those treated with antidepressants in placebo-controlled clinical trials in children.¹⁴

There is a political and social context to this affinity for antidepressants among some Americans. Kramer pointed this out when he described how his fluoxetine-treated patients felt more able to function in America's high-tech, high-energy society. (In fact, some called the stock market frenzy of the late 1990s the "prozac bubble" on the anecdotal assertion that many investors were taking antidepressants.¹⁵) America is a busy society, one in which people engage in many activities with a premium placed on doing. This has been called "American mania."¹⁶ The average American only sleeps 6.8 hours/night, even though the biological norm is 8–9 hours/night.¹⁷ Economists like John Kenneth Galbraith and sociologists like Thorstein Veblen and Max Weber (not to mention Karl Marx) have long pointed out that our modern American capitalist society emphasizes being productive, active, and energetic.¹⁸ Further, it deals with commodities, things that are bought and sold; much human activity is handled, for better or worse, as a commodity. The mechanism of advancing the sale of commodities is marketing. Thus, Americans vacation using travel packages put together by airline and hotel companies; they dress in styles influenced by clothing companies; they eat food options provided by large meat industries. In this social setting it would not be surprising for it to feel natural to take another commodity, such as a pill marketed by its own industry, that held promise to directly and immediately increase energy, activity, and productive behavior.

In this sense, antidepressants are simply the pharmaceutical manifestation of the American pursuit of happiness. If this is true, then feelings about antidepressants by patients and psychiatrists will be heavily influenced by many, often preconscious, social assumptions.

THE DECLINE OF PSYCHOPHARMACOLOGY

A consequence of this rush to use antidepressants has been a coarsening of the nature of psychiatric practice. Today, most psychiatrists practice psychopharmacology, not psychotherapy. However, psychiatrists do not have a clear rationale for the practice of psychopharmacology, such as when to prescribe, when not to prescribe, and why. This article seeks to provide such a rationale, as the author has done elsewhere,^{19,20} especially in relation to bipolar disorder.

Historically, it is important to first note that in the past, when psychopharmacology was still meekly knocking at the door of mainstream psychiatry, the general perspective was that psychoanalysis got to the heart of the matter; it cured. Medications, in contrast, only provided palliative symptom cover-up effects.

This viewpoint persists today in the minds of those who view medications as merely ways to improve symptoms rather than to treat disease. Thus, we see that many clinicians, despite using *DSM* diagnoses for insurance purposes, are symptom oriented. If a patient is depressed, the clinician will prescribe antidepressants; if a patient is anxious, anxiolytics will be prescribed; if a patient is labile, mood stabilizers will be prescribed; stimulants will be prescribed for a patient who is tired; if a patient is distracted, amphetamines will be prescribed; if a patient has insomnia, hypnotics will be prescribed. This is 19th century medicine, hardly worthy of being called scientific.

Psychopharmacology has become a game of listing symptoms and giving drugs that combat that symptom.¹⁹ This is unscientific but simple, no doubt partly responsible for the drive by non-physicians (such as psychologists and nurses) to be given prescribing privileges. "Med checks," 10-minute visits, and rapid and constant medication changes are features that characterize what psychopharmacologists believe they should do. While influenced by the managed care and pharmaceutical industries, clinicians need to bear some responsibility for simply going along with this haphazard approach to practice.

Besides being overly symptom-oriented, as opposed to diagnosis-based, the poor state of psychopharmacology practice today is also characterized by a lack of attention to research regarding efficacy. This can be called "Neurontin syndrome"—psychiatrists simply prescribe drugs they believe to be safe, regardless if there is much reason to believe they work. Antidepressants, viewed as harmless, are thus widely used to treat bipolar disorder in preference to infinitely better proven agents like lithium.

This article later outlines a philosophy of psychopharmacology that can provide a scientific rationale for practice that is sorely lacking today.

RISE OF THE CONTROVERSY

During the last few decades, as depression conferences proliferated and antidepressant sales surged, some clinicians and researchers began to observe poor outcomes with antidepressants in patients with bipolar disorder. They began to return to Kraepelin, questioning the *DSM-III*⁰ polarity-based approach to diagnosis.

In the 1970s, one of the first psychiatrists to make these observations was Athanasios Koukopoulos, MD. Working in an active clinical practice in Rome, Italy, he observed rapid-cycling occur with antidepressant use in bipolar disorder.²¹ His observations were consistent with those made around the same time by researchers at the National Institute of Mental Health (NIMH).²²⁻²⁴ The description of these observations in Goodwin and Jamison's widely-read text, *Manic-Depressive Illness*,²⁵ along with problems seen with the widespread

usage of new-generation antidepressants in the 1990s, led to increasing attention to the matter by other researchers.

The first observations by Koukopoulos were clinical in nature, and thus non-randomized. The NIMH group tested the possible link between TCAs and rapid cycling in a double-blind, placebo-controlled, on-off-on paradigm, and found that approximately 20% of their rapid-cycling bipolar patients experienced worsened cycling with antidepressants.²⁵ To this day, this study remains the only double-blind study to assess this matter.

Other observational reports in the last decade have both agreed²⁶⁻²⁹ and conflicted³⁰⁻³³ with the original concerns of Koukopoulos and the NIMH group. One reason observational data can provide conflicting results is due to the presence of confounding factors, ie, other factors which may explain the results but are not recognized or controlled in the statistical analysis. In the absence of randomization (which automatically removes confounding factors), statistical methods like multivariate regression models can help reduce such confounding bias. Unfortunately, almost none of the observational studies on this topic have attempted any method to reduce relevant confounding factors. For example, a frequently cited report by Coryell and colleagues³³ suggested that antidepressants are not associated with rapid cycling because when the index polarity was included in a regression model, depressive index polarity was statistically associated with rapid cycling, the effect of antidepressants no longer being notable. However, the investigators did not include any of a number of other potential confounding factors in their regression model, such as age, gender, substance abuse, past psychosis, number of depressive or manic episodes in the past, or age of onset. These factors might be related to later rapid cycling; thus, the actual effect of antidepressants, independent of these factors, remains unclear.

Another much-cited study³¹ by the Stanley Foundation also claims long-term benefit with antidepressants. Altshuler and colleagues³¹ initially compared the risk of depressive recurrence in bipolar patients who stopped using antidepressants in combination with mood stabilizers, versus patients who did not interrupt antidepressants. The interruption of antidepressants was associated with a high risk of depressive recurrence, while the continuation of these drugs for the entire period of the study was not associated with a high risk of (hypo)manic switch. Importantly, though, this observational study made no attempt to statistically correct for confounding factors, such as varying prevalence of rapid-cycling in the two arms, reasons for discontinuation versus continuation of antidepressants by patients or clinicians, number of depressive or manic episodes, past antidepressant-induced mania, age of onset of illness, past substance abuse, or past psychosis. In correspondence, the investigators reported that no patients with rapid cycling were in the study, a point not mentioned in their article, which would be quite unusual given the typical prevalence of rapid-cycling illness. Nonetheless, the other confounding fac-

tors were not assessed, making any direct assessments of the effect of antidepressants highly liable to confounding bias.

Two randomized studies of the same topic find the opposite results to the above non-randomized reports. In the first study,³⁴ patients initially stabilized on lithium plus imipramine openly for acute bipolar depression were double-blind randomized to continuation of the combination or discontinuation of imipramine. Both groups had almost identical relapse rates at 1-year follow-up. In the second study,³⁵ patients initially stabilized on mood stabilizers (mostly lithium) plus antidepressants (mostly serotonin reuptake inhibitors [SRIs]) for acute bipolar depression were openly randomized to continue both agents or discontinue the antidepressant. In an interim analysis, both groups had identical relapse rates and very similar overall mood morbidity at 1-year follow-up. These latter data are preliminary and need to be reassessed when this ongoing study ends. Overall, however, the randomized data do not support increased risk of depressive relapse with antidepressant discontinuation in bipolar disorder.

A RECENT META-ANALYSIS

Other analyses of randomized studies have suggested efficacy with antidepressants for acute bipolar depression. In a recent meta-analysis,³⁶ the authors claimed clear evidence of benefit with antidepressants in bipolar disorder compared to placebo, and no risk of mania with them. However, many limitations exist to this analysis. First, the entire meta-analysis of placebo-controlled studies came down to five reports, a relatively small number for meta-analytic techniques. Second, only one study³⁷ was designed with equal concurrent lithium use in all arms. The other studies either had no mood stabilizers (n=3 studies) or imbalanced lithium usage (n=1 study). Thus, to the clinical question of whether antidepressants are more effective than lithium alone, only one study³⁷ was designed to answer the question, and it found no benefit with antidepressants given therapeutic lithium levels. It also found some evidence of increased risk of acute mania with imipramine, though not paroxetine. Thus, it may be suggested that the meta-analysis might demonstrate that antidepressants are more effective than nothing (placebo), but it does not demonstrate that an antidepressant plus mood stabilizer is more effective than a mood stabilizer alone. Further, those limited studies were not powered to assess risk of acute mania, and indeed, the best designed studies suggest a likely risk with TCAs.

Although it would seem reasonable to limit one's assessment of the risk of antidepressant-induced mania to randomized placebo-controlled trials, one limitation of this approach is that such trials are not primarily designed to assess this issue (they are mainly designed to assess efficacy). Thus, they are not powered to identify such serious though relatively infrequent (if present $\leq 20\%$ of the time) side effects. Furthermore, side effects are frequently under-

estimated in clinical trials because of numerous exclusion criteria that screen out those with risk factors for serious side effects. In the case of antidepressant-induced mania, some potential risk factors such as substance abuse³⁸ are common exclusion criteria, which could lead to a serious underestimation of this risk in randomized studies. This is a common issue with side effects, as demonstrated in the past with the problem of sexual dysfunction with SRIs and more recently with the issue of suicidality and SRIs. In both those cases, the randomized clinical trial data underestimated or explained away either common (sexual dysfunction) or serious (suicidality) side effects. This is why large-scale observational experience is a legitimate means of exploring such side effects, and one should not feel limited to randomized data in this context.

MAINTENANCE EFFICACY OF ANTIDEPRESSANTS

In contrast to the above meta-analysis, which was limited to acute bipolar depression, one cannot assume that any such putative acute efficacy would translate into long-term maintenance

efficacy in prevention of a new mood episode. Ghaemi and colleagues^{34,35,39-47} conducted such a systematic review a few years ago. That review contained data from seven published, controlled, long-term, double-blind studies of antidepressants in bipolar disorder (mostly type I). Five studies were with TCAs, one with fluoxetine, and one with bupropion. This review has been updated below (Table 1).^{34,35,39-47} All of the studies with lithium comparison arms (all involving TCAs) showed antidepressants equal or less effective compared to lithium alone. Moreover, one of these studies (n=75)⁴¹ reported a long-term deterioration with antidepressants with increasing frequency of manic episodes (24% with imipramine plus lithium versus 10.5% with lithium alone) with no reduction in depressive episodes compared to lithium monotherapy (8% versus 10.5%). The lack of efficacy with TCAs bodes ill for SRIs and other novel antidepressants, which have never been proven more effective than TCAs in any mood disorder. It was concluded that TCAs appear to have relatively low efficacy in the prevention of depression in bipolar disorder, and further, one cannot assume that SRIs have any better efficacy.

In these prophylaxis studies of antidepressants in bipolar disorder, reanalysis with the use of confidence intervals fails to provide

TABLE 1
DOUBLE-BLIND RANDOMIZED CLINICAL TRIALS OF LONG-TERM ANTIDEPRESSANT TREATMENT IN BIPOLAR DISORDERS^{34,35,39-47}

| <i>Authors</i> | <i>N</i> | <i>Treatments</i> | <i>Findings</i> |
|-------------------------------|----------|---|--|
| Prien et al ³⁴ | 117 | Li vs. Li+IMI vs. IMI | With outcome measured as RDC episodes (duration up to 24 months), efficacy of lithium was equal to lithium plus imipramine |
| Ghaemi et al ³⁵ | 69 | Modern antidepressants plus mood stabilizers vs. mood stabilizers alone | Open, not blinded, only randomized discontinuation study with modern antidepressants. No benefit to antidepressant continuation |
| Prien et al ³⁹ | 44 | Li vs. IMI vs. PBO | With outcome measured as hospitalization or switch to new treatment, after 24 months lithium was more effective than imipramine which was equal in efficacy to placebo |
| Wehr et al ⁴⁰ | 5 | Li vs. Li+DMI | With outcome measured by nurse ratings, efficacy (mean 19 month duration) of lithium plus DMI was greater than lithium alone, but the switch and cycling rate with lithium plus DMI was also much higher |
| Quitkin et al ⁴¹ | 75 | Li vs. Li+IMI | After a mean of 19 months of treatment, with the outcome measured with RDC episodes, ⁴² lithium was equal in efficacy to IMI |
| Kane et al ⁴³ | 27 | Li vs. IMI vs. Li+IMI vs. PBO | Efficacy of lithium (mean duration 11 months) greater than IMI which was equal in efficacy to placebo |
| Sachs et al ⁴⁴ | 15 | BUP vs. DMI | Li plus BUP was equal in efficacy to lithium plus DMI (duration up to 12 months) with outcome measured as <i>DSM-III-R</i> ⁴⁵ episodes |
| Amsterdam et al ⁴⁶ | 80 | FLX vs. PBO in BP II and UP | With outcome measured as <i>DSM-III-R</i> episodes, FLX efficacy was similar in BP II and UP, with the switch rate higher in BP II (duration up to 14 months) |
| Leverich et al ⁴⁷ | 159 | BUP vs. SERT vs. VEN added to mood stabilizers | Blinded, no placebo, more acute manic switch with venlafaxine, overall only approximately 25% remission at 1 year with any antidepressant |

Li=lithium; vs.=versus; IMI=imipramine; RDC=Research Diagnostic Criteria; PBO=placebo; DMI=desipramine; BUP=bupropion; *DSM-III-R*=*Diagnostic and Statistical Manual of Mental Disorders*, Third Edition-Revised; FLX=fluoxetine; BP II=bipolar type II; UP=unipolar depression; SERT=sertraline; VEN=venlafaxine.

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evidence of the likelihood of type II error. For instance, in the study mentioned above,⁴¹ where depressive relapse was 8% with imipramine plus lithium versus 10.5% with lithium alone, the risk ratio is 0.77 with very wide confidence intervals (0.18, 3.21) extending in both directions around the null (1.0), thus suggesting no likely real effect. In another prophylaxis study,³⁴ remission rates were exactly the same (33%) with lithium plus imipramine versus lithium alone, resulting in a risk ratio of 1.0 and, again, very wide confidence intervals (0.53, 1.88). This re-analysis indicates that the absence of added benefit with antidepressants is unlikely to be due to low statistical power.

Since that review, the two small studies with new antidepressants have been supplemented by two larger randomized studies of modern antidepressants. In one study by the Stanley Foundation (n=159),⁴⁷ sertraline, bupropion, and venlafaxine were equally limited in efficacy when added to standard mood stabilizers for 1-year follow-up. Approximately 25% of patients experienced persistent remission without manic switch. Acute manic switch was more than two times more common with venlafaxine. In a second study, presented as an interim analysis, Ghaemi and colleagues³⁵ conducted an open randomized discontinuation study as part of the NIMH-sponsored Systematic Treatment Enhancement Program for Bipolar Disorder study. After initial recovery with a mood stabilizer plus antidepressant for acute bipolar depression, continuation of the antidepressant (compared to stopping it 2 months later) did not lead to any long-term benefit in mood morbidity, whether for depression or mania.

THE BATTLE OF THE GUIDELINES

Until the last few years, with the exceptions described above, antidepressant use in bipolar disorder was little questioned in academic circles, much as most clinicians appear to continue to use them extensively in practice. This initial consensus is reflected in the 1994 American Psychiatric Association Treatment Guidelines for bipolar disorder,⁴⁸ which recommended antidepressant plus lithium as first-line treatment from the beginning of the acute major depressive episode, with long-term continuation of both agents.

In 2002, with attention to the intervening research described above suggesting limited antidepressant efficacy and notable risks, a revision of the American Psychiatric Association Treatment Guidelines for bipolar disorder⁴⁹ moved antidepressants to a second-line choice, with lithium or lamotrigine alone as a first-line recommendation for acute and long-term treatment of bipolar depression.

This rather innocuous move has generated major backlash among some academics, particularly in Germany and England, who argue that the American guidelines unjustly de-emphasize antidepressant use. Those groups have since published conflicting

guidelines under the auspices of the World Psychiatric Association, strongly recommending antidepressant use for bipolar depression.⁵⁰ The Munich-based group published a critique which, in admirable Teutonic fashion, laid out its case quite clearly, asserting that the argument for restriction of antidepressants in United States guidelines is based on the following four premises.⁵¹ First, the risk of switching into mania/rapid cycling induced by antidepressants is an important clinical phenomenon in bipolar depression. Second, the risk of suicidality, suicide attempts, and suicide in bipolar depressive patients is of minor clinical relevance. Third, the antidepressive efficacy of antidepressants in bipolar depression is insufficiently proven. Last, antidepressive efficacy of mood stabilizers in bipolar depression is sufficiently proven.

Elsewhere, Ghaemi and colleagues³ re-examined those four assertions and reviewed the literature with attention to methodologic points that had not been attended to. It was concluded, based partly on the data provided above, that the Munich group was mistaken in its interpretation. Specifically, randomized data provide some evidence of increased risk of cycling with antidepressants. Further, the risk of suicide in bipolar depression can be taken as supportive of the use of lithium rather than antidepressants. In addition, there appears to be little evidence of antidepressants being more effective than lithium or lamotrigine in the treatment of acute bipolar depression and even less evidence as to antidepressant efficacy in longer-term treatment in prevention of depressive relapse. Lastly, the evidence reviewed leads us to the conclusion that mood stabilizers, particularly lithium and lamotrigine, are effective both in the treatment of acute bipolar depression and in the prevention of future depressive relapse episodes.

Some colleagues have interpreted the controversy in an almost postmodern manner, concluding that the experts are drawing opposite interpretations from the same data. In reality, as in most controversies (whether about medicine or art history), a selective review of the literature can support any perspective. The Munich group, in a highly selective fashion, used data which supported their perspective, without applying standard criteria of scientific judgment (such as the higher validity of randomized as opposed to observational data). The study by Ghaemi and colleagues³ attempted to apply a widely accepted methodologic rationale for interpretation of the data.

WHEN VERSUS IF

Ultimately, the controversy over antidepressant use is not that antidepressants should never be used or that they should always be used. Rather, the issue is how frequently and for what duration should antidepressants be used in treating bipolar disorder. In practice, both in the US (despite North American guidelines) and in Europe, the majority of patients with bipolar disorder regularly receive antidepressants (50% to 80%), usually long-

term.²⁶ I advocate a reversal of prescription patterns such that antidepressants would be used mostly short term and in a minority of patients (perhaps 20% to 40%).⁵² Clearly, further research is urgently needed to clarify these controversies, especially as to the long-term risks of mood destabilization with new antidepressants, as well as the relative risks versus benefits of antidepressants in bipolar type II disorder versus type I.

However, beyond the usual recommendation of more research, the continuation of this controversy reflects not so much how one interprets the data, but rather differences in underlying philosophies about psychopharmacology.

TOWARD A HIPPOCRATIC PSYCHOPHARMACOLOGY

It is important to discuss why and when clinicians prescribe medications, ie, a rationale for psychopharmacology. Today, clinicians practice without such a rationale, leading to highly aggressive, symptom-oriented treatment. This has led to extensive use of antidepressants in general, with empirical evidence most unfavorable to benefit with such use in bipolar disorder. How can this practice be turned around?

Perhaps this can be done by following two rules of psychopharmacology derived from the history of medicine, and by truly understanding (and not simply parroting) the Hippocratic approach to medicine.

The first step is to replace as much as possible symptom-oriented treatment with disease-oriented treatment. In other words, diagnoses are stand-ins for disease-entities; bipolar disorder can be seen as a disease entity. The treatment for that disease is mood-stabilizing medication like lithium, not antipsychotics for manic symptoms or antidepressants for depressive symptoms.⁵³ This can be referred to as Osler's Rule, in honor of Sir William Osler, who fought to move medicine from a symptom to a disease orientation.^{19,54,55}

The second step is to put an end to "Neurontin syndrome" by focusing on efficacy, not safety, when prescribing medications. Obviously, safety is relevant, but only after efficacy has been established. If a drug is not effective, then safety is irrelevant since there is no reason to prescribe. Oliver Wendell Holmes made this point in the 19th century in his fight against the homeopathy movement, which sought to treat patients with infinitesimal doses of ineffective treatments. They were clearly safe, but unnecessary.^{19,56} In bipolar disorder, the evidence for efficacy with antidepressants is minimal acutely and none in maintenance. Thus, their side-effect benefits are of little consequence.

When one puts together Osler's and Holmes' Rules, one can begin to see a rationale for the practice of psychopharmacology (Table 2). What is left is to apply these rules in a context of a belief about the nature of disease and health. Here is

where the philosophy of Hippocrates, which both Osler and Holmes promulgated, is key.

Hippocrates is often misunderstood.⁵⁶⁻⁵⁸ His main teaching was not, "First do no harm." Often that phrase is parroted as if it simply refers to an ethical conservatism in treatment. However, Hippocrates had a conceptual rationale for his ethics, one based on his beliefs regarding the nature of disease. In the Hippocratic perspective, disease, though produced by nature, was also cured by nature. Thus, nature was seen as the doctor's ally, not the doctor's enemy. Unlike the surgeon, for whom cure was achieved by the artificial means of the knife, the physician served as the handmaiden to nature, not curing, but helping nature to heal.

Thus, if bipolar disorder is viewed objectively, it can be characterized by spontaneous remission. Every episode goes away, and in fact usually quickly, with the average depression lasting (untreated, by natural history) half as long as unipolar depression (approximately 3–6 months versus 6–12 months in the latter), and the average mania only lasting on average ≤ 2 months. The problem with bipolar disorder is not so much treatment of the acute episode, since nature will ultimately treat it, but rather prevention of new episodes. The episodes go away, but they always come back.

The goal of treatment, then, is to help nature in the long-term process of reducing the frequency and severity of mood episodes; bipolar disorder is a longitudinal illness of recurrence; its treatment requires a long-term perspective. Thus, a Hippocratic perspective would require a good understanding of the illness, its natural history, and an appreciation of the beneficial role of natural recovery, always only using treatments that help and do not hinder that process. If indeed, as seems the case, antidepressants speed up the cycling and frequency of episodes in bipolar disorder, then they are an anti-Hippocratic treatment, worsening the illness rather than improving it.

Hippocratic psychopharmacology in general would be conservative and informed by the natural history of disease, not on abstract ethical grounds, but due to the nature of disease and health. Hippocratic psychopharmacologists would not constantly be at war with symptoms, trying to fight against nature as the enemy and believing that pills are directly the source of cure (or even, in the long run, the source of reducing symptoms). Rather, Hippocratic psychopharmacology would consist of, first and foremost, seeking to know the disease (Osler's rule), treat it only when the benefits clearly outweigh the risks (Holmes' rule), and doing so with a general humility that grows from knowing

TABLE 2
RULES FOR A HIPPOCRATIC PSYCHOPHARMACOLOGY¹⁹

| | |
|--------------|--|
| Osler's Rule | Treat diseases, not symptoms. |
| Holmes' Rule | Prescribe based on efficacy first, not safety. |

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that nature effects healing, with the clinician's role being to help when possible and to get out of the way when needed.

Contemporary psychopharmacology, it can be asserted, is anti-Hippocratic not on ethical grounds and not because doctors do not want to minimize harm. Rather, it is anti-Hippocratic on conceptual grounds, because most doctors either do not understand or implicitly reject the Hippocratic philosophy of disease and treatment.

CONCLUSION: EVIDENCE VERSUS BELIEF

In the end, this controversy is unlikely to be resolved by evidence because of the major influence of common beliefs about psychopharmacology. Among the relevant beliefs is a feeling among many Americans that favors being active and highly energetic, and an economic drive for a pharmacologic means of achieving that state of well-being and productivity. Further, psychiatrists have lapsed into a largely unscientific practice of psychopharmacology, often unaffected by evidence and driven by a symptom-based orientation to treatment. This approach to psychopharmacology breaks the maxims of the Hippocratic tradition of medicine, not simply on ethical grounds, but due to a lack of understanding of the relevance of the nature of disease and the role of the clinician in relation to nature in the healing process.

An objective assessment of the evidence regarding the use of antidepressants in bipolar disorder, combined with a Hippocratic approach to psychopharmacology, would seem to recommend more caution in the use of antidepressants for bipolar disorder. **PP**

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