The Use of Antidepressants in Bipolar Depression

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Contents

Abstract

Depression remains a significant debilitating and frequent phase of illness for patients with bipolar disorder. There are few FDA-approved medications for its treatment, only one of which includes a traditional antidepressant (olanzapine-fluoxetine combination), despite studies that demonstrate traditional antidepressants are one of the most commonly prescribed class of medications for bipolar patients in a depressive episode. While traditional antidepressants remain the primary option for treatment of unipolar depression, their use in bipolar depression has been controversial due to a limited efficacy evidence and the concern for potential harm. This chapter reviews the current data concerning the use of traditional antidepressants in bipolar disorder, and the current expert treatment guideline recommendations for their use.

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1 Introduction

The lifetime prevalence of bipolar disorders (BD) in the United States is approximately 4% (1% bipolar I disorder, 1% bipolar II disorder, and 2% subthreshold bipolar disorder) (Merikangas et al. 2007). While having a depressive episode at some point during the illness is not required for the diagnosis of bipolar I (BPI) disorder, over 90% will experience at least one depressive episode; most will experience multiple recurrent depressive episodes. In fact, BPI patients undergoing naturalistic treatment have been noted to have three times more depressive episodes than mania (Kupka et al. 2007), making depressive symptoms and depressive episodes the most common mood problem that BPI patients experience.

For bipolar II (BPII) patients, the struggle with depression is even greater. First, diagnostic criteria for BPII require that a patient have experienced at least one depressive episode in addition to a hypomanic episode. Second, naturalistic studies demonstrate that depressive episodes are 17 times more frequent than hypomania. This makes depressive symptoms and depressive episodes the most common mood state for BPII patients.

These depressive episodes in bipolar disorders are not benign. They are responsible for significant personal and occupational disruptions; they are complicated by multiple psychiatric and medical comorbidities; they are associated with cognitive dysfunction; and they are identified as a cause of shortened life expectancy (Post 2016).

Despite the high prevalence of bipolar depression and its severe consequences, there is a relative deficit in clinical treatment research compared with bipolar mania. Whereas in 2017, 12 medications were approved by the Food and Drug Administration (FDA) for bipolar mania, only 3 medications were approved for bipolar depression (lurasidone, olanzapine/fluoxetine combination, and quetiapine/quetiapine XR). None of the common "mood stabilizers" (carbamazepine, lamotrigine, lithium, valproate) have been approved by the FDA for the treatment of bipolar depression; nor have any of the antidepressants (with the exception of fluoxetine when used in combination with olanzapine).

The limited options of approved treatments have led to much discussion on what the optimal treatment algorithms should be in bipolar depression. In the late 1990s, conventional treatment of bipolar depression typically included antidepressant augmentation of mood stabilizers. But in the past two decades, there have been increasing concerns that use of antidepressants in BD may be both ineffective and potentially harmful to patients by causing switching from depression to mania (or inducing rapid cycling) (Fountoulakis 2010; Licht et al. 2008; Salvi et al. 2008).

Despite these concerns, traditional antidepressants continue to be the most commonly prescribed class of medication for bipolar depression, a finding documented

in several recent studies of practice patterns in both the United States (Baldessarini et al. 2007; Broeks et al. 2017; Hooshmand et al. 2018) and Europe (Greil et al. 2012; Karanti et al. 2016; Kessing et al. 2016). Recommendations for the use of traditional antidepressants in bipolar disorder are based on a clinical research literature that is often limited and inconsistent and which may run counterintuitive to many clinician's training and clinical experience (Pacchiarotti et al. 2013). Further, the level of recurrence and relapse of depression in patients with BD despite "adequate" treatment can be extremely challenging to both the patient and clinician. Thus, treatment choices are complicated by limited evidence-based data in the presence of a high-intensity, frequently relapsing disease. So not only is bipolar depression the most difficult-to-treat phase of bipolar disorder, there is also a rolling debate in psychiatry over the optimal treatment, particularly as to the role of traditional antidepressants in bipolar depression (Greil et al. 2012).

This raises the question of why are traditional antidepressants still so frequently used and what is their actual role in the treatment of bipolar depression.

This chapter will focus on the current literature for the efficacy and safety of antidepressant use in bipolar depression. What is the role of traditional antidepressants in bipolar disorder? Are they efficacious? Are they safe? It should be noted that this chapter will not review the current full recommendations for the treatment of bipolar depressions, but rather focus only on traditional antidepressant use in bipolar depression.

2 The Challenge of Differentiating Depression Diagnosis in MDD and BD

In previous editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), "bipolar" disorders and "unipolar" major depressive disorders were both listed under the general category of "mood disorders"; but in the DSM-5 (APA 2013), they have been separated into two distinct sections. This separation highlights the increasing scientific view that these two mood disorders are distinct entities, each with differing presumed causes, treatment responses, and courses of illness. However, the DSM-5 (as with previous versions) has continued to use identical symptom criteria for diagnosing depressive episodes in the context of either BD or unipolar MDD. The only difference is in the supporting criteria – primarily whether or not the patient has experienced an episode of mania/hypomania in the past. This use of similar diagnostic criteria highlights many clinicians' experiential view that these two disorders are essentially the same (Vöhringer and Perlis 2016). This separation of the mood disorder categories, but continued use of similar diagnostic criteria, presents clinicians with a unique clinical challenge: how to correctly identify and treat a depressive episode appropriately. And because most patients with BD present with the onset of depression, one-half to two-thirds are initially misdiagnosed (Lish et al. 1994; Hirschfeld et al. 2003).

As of yet, we do not have any clear biomarkers that can be used to discriminate depressive episodes in MDD and BD. This means that the most reliable strategy for clearer diagnostic certainty is in the observation of the longitudinal course of the

illness. By definition, if you follow the course of illness for a depressed patient long enough, all BD patients will at some point exhibit a hypomanic or manic episode. Obviously, in the midst of a depressive episode, this criterion is less helpful.

There are several other markers that may be helpful. Firstly, BD tends to manifest its symptoms earlier in patients' lives compared with MDD. A retrospective assessment of a large mood disorder cohort has found that roughly one-third of BD patients experience symptom onset prior to age 13 and another third experience symptoms between ages 13 and 18 (Perlis et al. 2004a, b). This finding, age of first episode, is among the most reliable features associated with BD risk and has been supported by numerous studies (Benazzi 2009; Pini et al. 2005; Perlis et al. 2006). Secondly, BD patients tend to receive more psychotropic medications over time due to multiple severe symptom episodes and more frequent recurrences (Swann et al. 2005; Angst et al. 2003). Thirdly, gender differences may be present between MDD and BD. Women are twice as likely as men to experience MDD while equally likely to experience BPI (Kessler et al. 2003).

However, none of these markers are clear-cut points that can be used to confirm the diagnosis. The number of people who struggle with MDD (lifetime prevalence 16.6%) far exceeds those with BPI (lifetime prevalence 1–3%). Thus age of onset and severity of illness observations are rather diluted by the larger sample populations. The most that can be said when seeing an individual patient is that the younger the onset of mood episodes or the more severe the symptoms, the greater should be the concern for BD. And as to the gender difference, it is complicated by the fact that in BPII patients, depressive episodes are not only significantly more common than hypomanic episodes, but the diagnosis is more prevalent in women than men (Hendrick et al. 2000).

There is a developing literature suggesting that bipolar and unipolar depressive episodes may be differentiated based on nosology. Although DSM-5 diagnostic criteria for major depressive episodes in the context of MDD and BPD are identical, there are selected clinical features that may be observed more often in MDD or BPD. Studies by Mitchell and colleagues found higher rates of atypical symptoms (such as hypersomnia, hyperphagia, and leaden paralysis) as well as psychomotor retardation, greater difficulty with cognition, more early morning awakening, more pronounced worsening of morning mood, and more frequent psychotic symptoms in bipolar depression relative to unipolar depression (Mitchell et al. 2008, 2011). Other researchers have suggested that irritability or "anger attacks" may be a marker of a mixed episode bipolar depression (Perlis et al. 2004a, b; Goodwin and Jamison 2007). Studies also suggest subtle differences between symptom profiles across disorders. For instance, atypical neurovegetative symptoms (hypersomnia and hyperphagia) may be more prevalent in BDII depressive episodes (Benazzi 2003). Another study showed that BDII patients, compared with MDD patients, had more prevalent suicidality and higher levels of psychomotor restlessness and agitation (Hantouche and Akiskal 2005). However, these symptoms may be subtle, and Vöhringer and Perlis (2016) note that clinicians who seek a single rating scale or group of clinical features that reliably distinguish BPD from MDD during the depressive phase of illness are likely to be disappointed.

Thus, only longitudinal follow-up truly allows for reliable diagnosis when individuals present in a depressive episode. For both clinicians and patients, a willingness to recognize that any initial diagnosis is provisional, subject to later reexamination, could help to diminish the rates and consequences of misdiagnosis of these two disorders.

Yet it remains important that MDD and BD be differentiated because there is predictive validity in making the correct diagnosis. The diagnosis conveys important information about the prospective course of the illness and the probable treatment selection/response. In general, MDD responds robustly to traditional antidepressants, whereas BD episodes do not.

3 Effectiveness of Traditional Antidepressants in Bipolar Depression

3.1 Efficacy of Antidepressants as Monotherapy

Most treatment guidelines and consensus statements of the past decade have routinely recommended that antidepressant monotherapy should be avoided in BPI (Pacchiarotti et al. 2013) (Table 1). The reasoning reflects concerns about the possibility of inducing a switch in the mood episode and that antidepressant monotherapy could worsen the course of the mood disorder with more frequent episodes and decreased periods of wellness (see Sect. 4 on Adverse Effects below) (Goldberg and Truman 2003). However, this position does not address whether antidepressant monotherapy is effective. There have been a few studies published that have evaluated efficacy of antidepressant monotherapy in bipolar depression.

Bipolar I Depression Amsterdam and Shults (2005) randomized 34 bipolar depressed patients to either fluoxetine (10–30 mg), olanzapine (5–20 mg), and olanzapine/fluoxetine (5–15 mg/10–40 mg) combination or placebo over an 8-week trial. A significant reduction in depressive symptoms was noted with all active treatments but no difference between treatments. Further, in their study acute treatment trial, there was no evidence of increased treatment-emergent manic symptoms. Unfortunately, this study was very small, representing less than ten patients per treatment arm.

The EMBOLDEN II study (McElroy et al. 2010), evaluating the efficacy of quetiapine in BD, randomized a total of 740 depressed bipolar patients (478 bipolar I, 262 bipolar II) to either monotherapy paroxetine (20 mg), quetiapine (300 or 600 mg), or placebo. After 8 weeks, quetiapine monotherapy was found to be effective in treating depressive symptoms, but there was no significant change in MADRS total score for paroxetine monotherapy compared with placebo. As for the potential switch to mania with monotherapy antidepressant use, there was no difference between paroxetine and placebo (10.7 and 8.9%), though it should be noted that the switch rate was much lower with quetiapine compared with paroxetine and placebo. The author's conclusion was

Table 1 Randomized, placebo-controlled clinical trials of traditional antidepressants used for the acute treatment of bipolar depression

	N	Bipolar type	Treatment arms	Duration (weeks)	Outcome measure	Results
Mendlewicz and Youdim (1980)	58 (34 with BP)	BP (Feighner criteria)	Deprenil + 5-HTP + benzerazide, or 5-HTP + benzerazide, or placebo	5	HDRS	DPL + 5-HTP was more effective than PBO
Himmelhoch et al. (1982)	59 (29 with BP)	DSM-III BPI (10) and BPII (19)	Tranylcypromine or placebo	10	CGI score	TCP more effective than PBO
Cohn et al. (1989)	89	DSM-III BD	Fluoxetine, or imipramine, or placebo Note: Lithium used concomitantly by 25% of sample	6	HADRS	FLX was more effective than IMI, which was more effective than PBO
Nemeroff et al. (2001)	117	DSM-III-R BDI	Imipramine + lithium, or paroxetine + lithium, or placebo + lithium Note: Some patients may also have received carbamazepine or valproate in addition to lithium	10	≤7 HDRS; ≤2 CGI	PXT and IMI augmentation were more effective than PBO at low LI levels; no difference at high LI levels
Tohen et al. (2003)	833	DSM-IV BDI	Olanzapine monotherapy, or olanzapine/fluoxetine combination, or placebo	8	MADRS	OLZ is more effective than PBO; OLZ/FLX is more effective than either OLZ or PBO
Shelton and Stahl (2004)	30	DSM-IV BDI (21) and BDII (9)	MS + paroxetine + placebo, or MS + risperidone + placebo, or MS + paroxetine + risperidone Note: MS could be valproate, lithium, carbamazepine, or topiramate	12	HDRS-17	No significant differences among treatment groups
Amsterdam and Shults (2005)	34	DSM-IV BDI (32) and BDII (2)	Olanzapine monotherapy, or fluoxetine monotherapy, or olanzapine/fluoxetine combination, or placebo	8	HDRS	No significant differences among active treatment groups. All were superior to PBO
Sachs et al. (2007)	366	DSM-IV BDI (240) and BDII (114)	MS + paroxetine, or MS + bupropion, or MS + placebo Note: MS could be lithium, valproate, carbamazepine, or atypical antipsychotic	26	Clinical monitoring form	No significant difference. Nonsignificant trend favored MS + PBO

Yatham et al. (2016)	344	DSM-IV BPI	MS + agomelatine, or MS + placebo Note: MS could be lithium or valproate	8 and 52	MADRS	No significant difference
Ghaemi (2015)	119	DSM-IV BPI (75) and BDII (44)	MS + citalopram, or MS + placebo Note: MS could be lithium, valproate, carbamazepine, antipsychotic, lamotrigine, or a combination of above meds	6	MADRS	No significant difference

FLX fluoxetine, *IMI* imipramine, *LI* lithium, *MS* mood stabilizer, *OLZ* olanzapine, *PBO* placebo, *TCP* tranylcypromine

that although paroxetine monotherapy was not an efficacious treatment, it was not a high-risk acute treatment option (Amit and Weizman 2012).

Bipolar II Depression Traditionally, the potential risk of a hypomanic switch in BPII patients has been estimated to be lower than in BPI patients, but treatment guidelines have not endorsed antidepressant monotherapy due to the same concerns of treatment-emergent hypomania. There are a few published studies that have evaluated the efficacy of traditional antidepressants in BPII.

Amsterdam and Shults (2005) conducted an open-label study examining the response rate of fluoxetine monotherapy (10–80 mg) in 148 BPII depressed patients over 14 weeks. The response rate was 59.5% and the remission rate was 58.1%. Unfortunately 6 patients (4.1%) had treatment-emergent hypomanias (defined as a YMRS score $\geq$8), while 29 patients (19.6%) were noted to have a subsyndromal hypomania (defined as an episode lasting up to 3 days with 4 or more symptoms, or as an episode lasting $\geq$4 days with $\leq$3 symptoms). Despite this, the authors concluded that fluoxetine monotherapy was an effective and relatively safe short-term treatment for BPII depression.

Parker et al. (2006) randomized ten BPII depressed patients to escitalopram monotherapy in a double-blind, placebo-controlled crossover study lasting 9 months. The authors noted that the escitalopram treatment led to a significant reduction in depression severity, percentage of days depressed, and percentage of days impaired when compared with placebo. Further, they noted no indication that the SSRI led to a worsening of illness course.

Amsterdam and Shults (2008) randomized 83 BPII depressed patients to a 12-week open-label trial of either venlafaxine monotherapy or lithium monotherapy. Thirty-four venlafaxine-treated patients (79.1%) completed the trial, but only 15 of the lithium-treated patients (37.5%) did so ($P < 0.0005$). Venlafaxine monotherapy had both a greater reduction in HAM-D 28 scores (−6.57 points, 95% CI, −11.97 to −1.18; $p = 0.017$) and a larger proportion of treatment responders (58.1 vs 20.0%; $P < 0.0005$) and treatment remitters (44.2 vs 7.5%; $P < 0.0005$). The authors then switched 17 of the lithium nonresponders to venlafaxine. Results showed venlafaxine produced significantly greater reductions in HAM-D ($P < 0.0005$), CGI/S ($P < 0.0005$), and CGI/C ($P < 0.0005$) scores vs. prior lithium. There was no difference in mean YMRS scores between treatment conditions. In a follow-up study of venlafaxine versus lithium monotherapy in 129 BPII depressed subjects, Lorenzo-Luaces and Amsterdam (2018) reported venlafaxine was superior to lithium in reducing symptoms of depression during acute treatment; however, there were no significant differences between treatments in quality-of-life ratings.

Agosti and Stewart (2007) conducted a post hoc analysis of a double-blind study, which compared the relative efficacy of placebo, imipramine (average dose 250 mg/day), and phenelzine (average dose of 60 mg/day) in depressed outpatients. BPII depressed response rates were 57% for imipramine and 52% for phenelzine, compared with 23% in the placebo arm. No patient developed manic symptoms that required medication discontinuation or mood stabilizer augmentation.

Altshuler et al. (2017) conducted a 16-week, double-blind, multisite comparison study, in which 142 BPII depressed subjects were randomized to receive lithium monotherapy ($N = 49$), sertraline monotherapy ($N = 45$), or combination treatment with lithium and sertraline ($N = 48$). The treatment response rate for the overall sample was 62.7% ($N = 89$), without significant differences between groups.

3.2 Efficacy of Antidepressants as Adjuncts to Mood Stabilizers

Until 2002, all BP expert consensus guidelines recommended using antidepressants as first-line treatment for acute BP depression (Table 1). However, the American Psychiatric Association (APA) guidelines published in 2002 (APA 2002) recommended that lithium or lamotrigine should be first-line treatments and relegated antidepressants to second-line options. The authors expressed concern about the limited data demonstrating antidepressant efficacy and concerns that they may be associated with worsening of illness (Ghaemi et al. 2003).

In 2004, Gijsman et al. (2004) published a meta-analysis of 12 clinical trials in bipolar depression (1,088 patients) using antidepressants (SSRIs, TCAs, MAOIs) primarily as adjuncts to mood stabilizers. The main findings were that antidepressants were more effective than placebo as adjunctive therapy in trials up to 10 weeks, and that they did not induce more switching to mania (the rate for antidepressants was 3.8%; rate for placebo was 4.7%).

In a sub-analysis, the authors reviewed the five identified published trials that were placebo-controlled randomized comparisons with various antidepressants for the treatment of acute bipolar depressive episodes. It should be noted that most (about 75%) but not all of the subjects in the trials were also on a mood stabilizer or atypical antipsychotic. The five trials included the following:

1. Tohen et al. (2003) conducted a large registration study ($n = 456$) comparing olanzapine/fluoxetine combination ($n = 86$ at 6/25 mg, 6/50 mg, or 12/50 mg doses) or olanzapine monotherapy ($n = 370$ at 5–20 mg doses) with placebo ($n = 377$). Results showed that the olanzapine/fluoxetine combination was significantly better than olanzapine monotherapy, which was significantly better than placebo for treatment response. Remission criteria were met by 24.5% (87/355) of the placebo group, 32.8% (115/351) of the olanzapine group, and 48.8% (40/82) of the olanzapine-fluoxetine group. Treatment-emergent manic symptoms did not differ among the three groups (about 6% over the 8-week trial).
2. Cohn et al. (1989) evaluated fluoxetine ($n = 30$), imipramine ($n = 30$), or placebo ($n = 29$) in bipolar depression. They reported that 86% of the fluoxetine-treated patients responded (50% improved in HAM-D scores) compared with 57% of the imipramine-treated and 38% of the placebo-treated patients. Of note, only 22 of the 89 subjects were on concomitant lithium.
3. Himmelhoch et al. (1982) evaluated the use of tranylcypromine in anergic depressed patients. In their sample of 59 depressed patients, 10 were BPI and

19 were BPII. They noted that improvement on tranylcypromine after week 1 was greater than that on placebo after week 6.

4. Mendlewicz and Youdim (1980) studied the use of the MAOI L-deprenyl (in combination with L-5-HTP and benzerazide) versus placebo in 58 depressed patients (34 with BPD). They found a significant improvement for the combination therapy compared with placebo.
5. In the fifth trial, Nemeroff et al. (2001) compared the efficacy and safety of imipramine ($n = 39$) or paroxetine ($n = 35$) with placebo ($n = 43$) in the treatment of 117 BP depressed patients on stable doses of lithium. Results showed that there were no significant differences in the Hamilton depression scale or CGI severity of illness scale among the three groups. They did note that among patients with low serum lithium levels (<0.8 meq/l), paroxetine and imipramine were superior to placebo. They concluded that antidepressants may not be useful adjunctive therapy for BP depressed patients with high serum lithium levels, but may be beneficial for patients who cannot tolerate high serum lithium levels or have symptoms that are refractory to the antidepressant effects of lithium.

Gijsman et al. (2004) used these studies to evaluate antidepressant efficacy by clinical response (<50% improvement in HAM-D or MADRS or moderate-to-marked improvement in the CGI scale) and remission (defined as a HDRS ≤7 and a MADRS ≤12). The first four trials included data on clinical response. They calculated that of the 662 total patients (213 assigned to experimental group and 449 assigned to placebo group), there was a significant advantage in achieving response for the group treated with antidepressants compared with placebo (NNT = 4.2; 95% CI = 3.2–6.4). Only two of the studies (Tohen et al. 2003; Nemeroff et al. 2001) included data on remission. They calculated that of the 573 total patients (160 assigned to the experimental group and 413 assigned to the placebo group), there was a significant advantage for the group treated with antidepressants compared with placebo (NNT = 8.4; 95% CI = 4.8–33). Given the limited risk, the authors suggested that SSRIs may be an effective treatment for acute bipolar depression.

This study received a lot of discussion in the literature. Critics noted concerns that the studies included in the analysis were of short duration (4–10 weeks duration) and included a mixture of bipolar patients (including bipolar II depression or mixed episodes), thus potentially underestimating the risk of antidepressant-induced manias or further mood destabilization (Amit and Weizman 2012).

In 2011, Sidor and MacQueen published an updated meta-analysis of antidepressant use as augmentation treatment for acute bipolar depressions. They identified six additional studies that assessed antidepressant use in the acute treatment of bipolar depression that had been published since Gijsman's 2004 analysis. They combined this information with earlier studies for a total of 15 studies that contained 2,373 subjects. Their meta-analysis found that antidepressants were not statistically superior to placebo or mood stabilizers for acute bipolar depression. They also noted that

for studies that had more sensitive criteria to define a mood "switch," antidepressant use had higher rates than placebo or mood stabilizers.

Sidor and MacQueen also conducted a sub-analysis of six studies identified that were double-blind, placebo-controlled comparisons. These included three of the studies identified by Gijsman et al. (2004) (Tohen et al. (2003) study of olanzapine/fluoxetine, Cohn et al. (1989) study of fluoxetine and imipramine, and Nemeroff et al. (2001) study of imipramine and paroxetine), but they excluded two others (Himmelhoch et al. (1982) study of tranylcypromine and Mendlewicz and Youdim (1980) study of L-deprenyl) due to concerns that the studies did not distinguish between unipolar and bipolar patients in the outcome measures. Sidor and MacQueen also included three more recent placebo-controlled trials.

1. Shelton and Stahl (2004) conducted a trial of 30 BPI/BPII depressed patients who were receiving a stable dose of a mood stabilizer. They randomly assigned the patients to 12 weeks of double-blind treatment in one of three arms: risperidone (plus placebo), paroxetine (plus placebo), or risperidone plus paroxetine. All three groups experienced significant reductions in depression ratings from baseline to endpoint; but there were no significant differences between groups. The switch rate into mania or hypomania was very low, with only one patient in the paroxetine plus placebo condition experiencing mild hypomania.
2. In the study by Amsterdam and Shults (2005) (previously discussed in the antidepressant monotherapy section), 32 BPI and 2 BPII MDE patients were randomized to receive double-blind therapy with fluoxetine monotherapy 10–30 mg daily, olanzapine monotherapy 5–20 mg daily, combined therapy with fluoxetine 10–40 mg plus olanzapine 5–15 mg daily, or placebo for up to 8 weeks. There were significant reductions over time in mean HAM-D 28 and MADRS ratings for all treatment groups ($p < 0.006$). However, there were no differences among treatment conditions ($p =$ ns). There was no significant increase in YMRS scores over time in any treatment group. In contrast, there was a significant reduction in the mean YMRS score in the fluoxetine-treated patients over time ($p = 0.008$).
3. Sachs et al. (2007) published results from a clinical trial within the larger National Institute of Mental Health (NIMH) effectiveness study, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). As part of the trial, the investigators conducted a multicenter, double-blind, randomized, placebo-controlled study of either bupropion or paroxetine as adjuncts to treatment with a mood stabilizer (primarily lithium, valproate, or carbamazepine). 366 BPI and BPII subjects with depression were treated for up to 26 weeks. The primary outcome was the percentage of subjects in each treatment group who achieved durable recovery (8 consecutive weeks of euthymia). The authors did not find a significant difference between the groups that received adjunctive antidepressant treatment and the group that received only mood stabilizer plus placebo. 23.5% (42/179) of the subjects who received adjunctive antidepressant therapy to a mood stabilizer achieved durable recovery, while 27.3% (51/187) of subjects treated with mood stabilizer monotherapy achieved durable recovery. Further, the

rates of treatment-emergent mania were similar between the two groups. Overall, the authors concluded that use of adjunctive bupropion or paroxetine to mood stabilizers in bipolar depression was associated with neither increased efficacy nor increased risk of treatment-emergent affective switch.

Of the six double-blind, placebo-controlled clinical trials, four (Tohen et al. 2003; Shelton and Stahl 2004; Amsterdam and Shults 2005; Cohn et al. 1989) supported efficacy for antidepressants in bipolar depression, while two (Nemeroff et al. 2001; Sachs et al. 2007) did not. Sidor and MacQueen (2011) then conducted a meta-analysis of the five placebo-controlled trials that measured clinical response (all studies except Nemeroff et al. 2001). The pooled treatment effect for the 342 subjects treated with antidepressants compared to the 565 subjects treated with placebo revealed a small, but nonsignificant, benefit of antidepressant over placebo (relative risk = 1.18; 95% CI, 0.99–1.40; $p = 0.06$).

Sidor and MacQueen also conducted a meta-analysis the four studies (1,346 subjects) that assessed clinical remission (Tohen, Sachs, Shelton, Nemeroff). Results showed that subjects assigned to antidepressant treatment did not have a significantly better remission rate than those receiving placebo (RR = 1.20; 95% CI, 0.98–1.47; $p = 0.09$).

In 2013, Vázquez et al. (2013) also conducted a meta-analysis of placebo-controlled trials in acute bipolar depression that focused on or included an antidepressant treatment arm. They identified seven trials (with ten different comparison arms) meeting their inclusion criteria. These included five of the studies noted above (Cohn et al. 1989; Nemeroff et al. 2001; Tohen et al. 2003; Shelton and Stahl 2004; Sachs et al. 2007) but also included two studies that had an antidepressant monotherapy treatment arm (Agosti and Stewart 2007; McElroy et al. 2010) (see description of studies above). Their analysis found superiority of antidepressants over placebo (relative risk = 1.43, 95% CI = 1.11–1.84; $z = 2.76$, $p = 0.006$).

Finally, in 2016, McGirr and colleagues conducted the most recent meta-analysis of placebo-controlled trials in acute bipolar depression focused on second-generation antidepressants. They identified six trials (1,383 patients) for review. These included Nemeroff et al. (2001), Tohen et al. (2003), Shelton and Stahl (2004), and Sachs et al. (2007) as previously reviewed. In addition, they also included two studies completed in 2015.

1. Yatham et al. (2016) examined the efficacy of agomelatine (an antidepressant approved in Europe but not in the United States that has melatonin receptor agonist and 5HT2c receptor antagonist properties) versus placebo as adjuncts to lithium or valproate in bipolar depression. 344 subjects were enrolled for the 8-week trial. No significant differences in the improvement of depressive symptoms were observed between the two groups. Adverse events (including mood switching) were reported to be low and similar in both groups.
2. Ghaemi (2015) conducted a study of 119 BPI and BPII depressed subjects on a traditional mood stabilizer or atypical antipsychotic (or both). Subjects were

randomized to adjunctive citalopram or placebo for 6 weeks. No significant improvement was reported for the citalopram over placebo.

In their meta-analysis of these six studies, McGirr and colleagues found that second-generation antidepressants were associated with a small but significant improvement in clinician-rated depressive symptom scores, but there were no differences in clinical response and remission rates. They further found that there was no increased risk of treatment-emergent mania or hypomania during the acute treatment period. Based on the data, they calculated that adjunctive antidepressants in BP depression have a number needed to treat (NNT) of 15 and number needed to harm (NNH) of 19.

In a commentary on the study, Vieta and Garriga (2016) noted that though the analysis effect size was small, it was significantly affected by the agomelatine trial (Yatham et al. 2016) that had a large placebo response (53%) and increased risk of mood switching. If that trial were excluded from the analysis, it was estimated that the effect size would be larger and the switch rates even further reduced. Overall, they interpreted the data as suggesting that adjunctive antidepressant treatment efficacy is limited (though significant) and the tolerability is good (but risk remains significant).

Two naturalistic studies have evaluated possible predictors of who would respond to antidepressant treatment. Pacchiarotti et al. (2011a, b, c) found that a previous response to antidepressants was a good prognostic indicator of response to current antidepressant treatment. Post et al. (2012) found that a history of frequent antidepressant use in the past and a more severe course of illness were poor prognostic indicators of current antidepressant response.

3.3 Long-Term Use of Antidepressants in Bipolar Disorder

As noted previously, use of traditional antidepressants in bipolar disorder is common (Table 2). This would occur either for the acute treatment of BP depression (as noted above), or as prophylactic/maintenance treatment, or both. While there is no evidence that antidepressants may prevent manic episode relapse, there may be a prophylactic effect on depressive episodes.

Altshuler et al. (2003) followed 84 subjects who had achieved remission from their BP depression with the addition of an antidepressant to an ongoing mood stabilizer over a 1-year period. They found that patients who discontinued antidepressant treatment experienced a shorter latency to depressive relapse ($\chi^2 = 9.63$, $p = 0.002$) and were more likely to relapse (70% compared with 36%). In a later analysis, Altshuler et al. (2009) noted that the patients who had a good response to acute treatment with a mood stabilizer augmented by an antidepressant would probably maintain that response with the same continued treatment over a year's period of time. Patients who achieved only a partial acute antidepressant response were less likely to further improve when the same treatment was sustained.

Table 2 Randomized, placebo-controlled clinical trials of traditional antidepressants used for the long-term treatment of bipolar depression

	N	Bipolar type	Treatment arms	Duration (months)	Outcome measure	Result
Prien et al. (1973)	122 (44 with BP)	MDD and BPI	Imipramine monotherapy, or lithium monotherapy, or placebo	24	New manic or depressive episodes that required hospitalization or other medication intervention	In BP subjects, LI was significantly better at preventing recurrence than IMI or PBO
Quitkin et al. (1981)	75	BPI	Lithium + imipramine, or lithium + placebo	24	New manic or depressive episode	No significant difference between groups
Kane et al. (1982)	22	BPII	Lithium monotherapy, or imipramine monotherapy, or lithium + imipramine, or placebo	19	New manic or depressive episode	LI more effective in preventing relapse of either depression or hypomania in BPII compared to IMI or PBO
Prien et al. (1984)	114	BP	Lithium monotherapy, or imipramine monotherapy, or lithium + imipramine, or placebo	24	New manic or depressive episode, or poor response	LI and the LI/IMI treatments were superior to IMI in preventing manic recurrences and were as effective as IMI in preventing depressive episodes. LI/IMI combination provided no advantage over LI monotherapy
Johnstone et al. (1990)	40 (13 BP)	DSM-III-R BP and MDD	Lithium monotherapy, or lithium + amitriptyline	36	New manic or depressive episode	No significant difference between groups
Amsterdam and Shults (2010a, b)	81	DSM-IV BPII and NOS	Fluoxetine monotherapy, or lithium monotherapy, or placebo	8	New manic or depressive episode	Risk of relapse was significantly lower with FLX compared with LI. No difference in relapse time between LI and PBO
Ghaemi et al. (2010)	70	DSM-IV BPI	MS + continued antidepressant, or	36	Clinical monitoring form	AD continuation trended (but not clinically significant)

		(49) and BPII (21)	MS + discontinued antidepressant			toward less severe depressive symptoms and mildly delayed depressive episode relapse without increased manic symptoms. No benefits in prevalence or severity of new depressive or manic episodes, or overall time in remission, occurred

AD antidepressant, *FLX* fluoxetine, *IMI* imipramine, *LI* lithium, *MS* mood stabilizer, *OLZ* olanzapine, *PBO* placebo

Leverich et al. (2006) followed depressed bipolar patients who had responded to treatment with venlafaxine, bupropion, or sertraline added to standard mood stabilizers for up to 1 year. They found that only 15–25% had no further episodes, though there was no placebo arm for comparison.

Amsterdam and Shults (2010b) examined the safety and efficacy of long-term fluoxetine monotherapy, lithium monotherapy, and placebo therapy in preventing relapse and recurrence of BPII depressive episodes. They randomized 81 patients who had responded to an open-label fluoxetine monotherapy treatment study to receive 50 weeks of monotherapy with fluoxetine, lithium, or placebo. The risk of relapse and the length of time to relapse were significantly better for patients receiving fluoxetine compared with lithium and placebo. There were no differences in hypomanic symptoms among treatment groups.

In contrast, Ghaemi et al. (2010) conducted an antidepressant discontinuation randomization study as part of the STEP-BD program. They found that there was no significant symptomatic benefit, robust depressive episode prevention, or enhanced remission rates for patients who continued on long-term antidepressant treatment, but they did note that patients receiving antidepressants with mood stabilizers tended toward less severe depressive symptoms and mildly delayed depressive episode relapse without an increase in manic symptoms. It should be noted that a rapid cycling course predicted three times more depressive episodes with antidepressant continuation.

There have been a few meta-analyses on the efficacy of long-term antidepressant use in bipolar disorder. Ghaemi et al. (2008) conducted a meta-analysis of seven long-term trials (350 BP patients) that included antidepressants. They found that long-term antidepressant treatment was associated with a statistically significant and moderate reduction in the recurrence of depression compared to control (RR 0.73, 95% CI 0.55–0.97, $p = 0.03$, NNT = 11.1) but with a significant increased risk of mania (RR 1.72, 95% CI 1.23–2.41, $p = 0.002$, NNH = 7). There was no significant difference in new depression for antidepressants with or without mood stabilizers versus mood stabilizers, antidepressant with mood stabilizers versus mood stabilizers alone, and antidepressant versus mood stabilizers (three comparisons, $n = 118$). The authors concluded that compared with giving a mood stabilizer alone, adding an antidepressant yielded neither major protection from depression (RR = 0.84; 95% CI 0.56–1.27; NNT = 16) nor substantial increase in risk of mania (RR = 1.37; 95% CI 0.81–2.33; NNH = 16).

More recently, Liu et al. (2017) reviewed 11 trials with 692 bipolar disorder patients. Their analysis found that antidepressants were superior to placebo in reducing new depressive episodes without increasing the risk of new manic/hypomanic episodes either used as monotherapy or in combination with a mood stabilizer. Further, subgroup analyses suggested that these findings were more powerful for BPII than BPD I. However, the authors also noted that compared with mood stabilizer monotherapy, antidepressant monotherapy significantly increased the risk of affective switch with no improvement in prophylaxis of new depressive episodes. Overall, the authors concluded that long-term antidepressant treatment may reduce

new depressive episodes with no significantly increased risk of treatment-emergent mania/hypomania, particularly in BPII.

In contrast to these findings, Vöhringer et al. (2015) treated 21 BPI and 49 BPII depressed subjects with antidepressants plus mood stabilizers to sustained euthymia for 2 months. They conducted an open randomization to either continue or discontinue the antidepressants, following the patients for up to 3 years. They found that both BPI and BPII depressed patients showed improvement in depressive frequency when antidepressants were continued, but this finding was much stronger in BPI rather than BPII patients.

4 Adverse Events Associated with Traditional Antidepressants in Bipolar Disorder

4.1 Antidepressants and Mood Switching

The potential for antidepressants to induce a mood switch from depression to mania/hypomania has been well recognized since the introduction of tricyclics in the 1950s (Ball and Kiloh 1959; Leyberg and Denmark 1959). However, several questions remain as to their potential harm. These include: What is the exact risk for antidepressant switch? Are all antidepressants equal in their potential to induce mood switching, or do some have greater/less risk? Does the presence of a mood stabilizer decrease the risk of mood switching? Are certain types of bipolar disorder more likely to be associated with mood switching risk? Do antidepressants have the potential to cause increased frequency in mood cycling or worsening of the bipolar course?

The risk for antidepressant-induced switching is unclear. There are several reasons for this. First, because of the nature of BD, assessing causality of mood change to an antidepressant versus other causes (including the unpredictable spontaneous nature of the disease) is complicated (Licht et al. 2008). Second, randomized trials that report the mood switching have used multiple different criteria to define a mood switch (e.g., scale assessed change, investigator assessment, hospital admission) making comparisons difficult to interpret (Fornaro et al. 2018). Further, the term "switching" probably does not fully capture the full range of concerns that include symptom aggravation (from the development of subsyndromal symptoms to full-episode mania switch) or the potential longer-term alterations of episode frequency or amplitude (Berk et al. 2010). Because of this, the recent International Society of Bipolar Disorders' (ISBD) consensus guidelines have recommended using the term "treatment-emergent affective switch" instead of antidepressant-induced switch (Tohen et al. 2009), to emphasize association without implying causality.

Studies reporting switch rates of antidepressant use in bipolar depression have been mixed. Some have found associations (Altshuler et al. 1995; Boerlin et al. 1998; Peet 1994; Prien et al. 1973; Truman et al. 2007; Valentí et al. 2012), while others have not (Angst 1985; Lewis and Winokur 1982; Visser and Van Der Mast

2005). Tondo et al. (2010) conducted a meta-analysis review of 35 studies that included data on mood switching, type of antidepressant used, and the presence of mood stabilizers. They found that overall risk of spontaneous switching in BP depressed patients to hypomania or mania was high (13.8%), but the risk of switching in patients taking antidepressants was only slightly higher (15.3%). Sidor and MacQueen (2011) found pooled switch rates of 8% with either antidepressant or placebo treatment in research clinical trials for bipolar depression, indicating no difference between spontaneous and antidepressant-associated risks. Fornaro et al. (2018) found the cumulative incidence of treatment-emergent mania among an identified 1,316 BP depressed subjects over 20 randomized controlled trials (RCTs) was 11.8%. In the STEP-BD trial, Sachs et al. (2007) reported that in the 6-month double-blind placebo-controlled trial, rates of mood elevations were indistinguishable (10.1% compared with 10.7%) between subjects receiving a mood stabilizer plus an antidepressant (bupropion or paroxetine, $N = 179$) and those receiving a mood stabilizer plus placebo ($N = 197$).

However, these studies should be cautiously interpreted because observation studies consistently find higher levels of manic switching compared with randomized clinical trials. For example, whereas Fornaro et al. (2018) found in their meta-analysis of placebo-controlled clinical trials that only 11.8% had treatment-emergent mania, they noted that the cumulative incidence of treatment-emergent mania among 1929 patients with BD over 12 prospective open studies was 14.4%, while the cumulative incidence of treatment-emergent mania among 4,767 patients with BD over 15 retrospective studies was 30.9%. Allain et al. (2017) have suggested that these disparate findings suggest either randomized clinical trials underestimate mood switching or observational studies overestimate mood switching.

Several meta-analyses reviewed previously have evaluated specific antidepressant-associated switch risk. Peet (1994) reported that the rate of treatment-emergent switch occurred substantially more often with tri- and tetracyclics (11.2%) than with SSRIs (3.7%) or placebo (4.2%). Gijsman et al. (2004) noted in their meta-analysis that with the exception of tri- and tetracyclics and venlafaxine, switching was uncommon. Tondo et al. (2010) noted that though the risk of mood switching was not significantly different in patients on antidepressant from those not taking antidepressants, tri- and tetracyclics carried a higher risk for new mania/hypomania than SSRIs or MAO inhibitors. Finally, Sidor and MacQueen (2011) found that SSRIs and bupropion were not associated with more switching than placebo during short-term treatment, but noted that studies employing sensitive criteria to define switching reported higher switch rates for tri- and tetracyclics and venlafaxine than for SSRIs and bupropion. These studies suggest that tricyclic, tetracyclic, and SNRI antidepressants may have a higher risk of inducing mood switches than most SSRIs (see also Vázquez et al. 2013; Tondo et al. 2010; Post et al. 2006; Vieta et al. 2002).

There is limited evidence about the protective effects mood stabilizers may have in preventing mania/hypomania during treatment with antidepressants. In their comprehensive review, Tondo et al. (2010) found a lack of evidence that treatment with mood stabilizers protects against mood elevation in bipolar patients, with or

without antidepressant co-treatment, but they also cautioned that there is a lack of appropriate controls or randomization with which to make an adequate assessment. In contrast, a more recent study by Viktorin et al. (2014) used the Swedish national registries to identify 3,240 patients with bipolar disorder who started treatment with an antidepressant (2005–2009). Amazingly, they discovered that 35% of the identified bipolar patients were being treated with antidepressant monotherapy. Their analysis determined that the increased risk of treatment-emergent mania was confined to patients on antidepressant monotherapy (2.83, 95% CI = 1.12, 7.19). Patients treated with antidepressants who also were taking a mood stabilizer did not appear to have that risk (0.79, 95% CI = 0.54, 1.15). The limited risk of switching in the mood stabilizer augmented group appeared to further decrease after the first 3 months of treatment.

Clinical experience has noted that the risk of switch may also vary according to bipolar type. Early research suggested that patients with BPII are at lower risk of switching than those with BPI (Himmelhoch et al. 1982; Amsterdam et al. 1998; Parker et al. 2006; Amsterdam and Shults 2010a, b). This finding was supported in a post hoc analysis from the Stanley Foundation Bipolar Network study (Altshuler et al. 2006) and a systematic meta-analysis review of 13 prospective studies (Bond et al. 2008) in BPI and BPII depression.

Factors that may be associated with a higher risk of switching include previous antidepressant-induced mood switching, rapid cycling, younger age of onset, comorbid anxiety or substance use disorders, subsyndromal manic symptoms, and number of previous manic episodes (Gorwood et al. 2016; Scott et al. 2017; see Vázquez et al. 2013 for a more complete discussion). Pacchiarotti et al. (2011a, b, c) found that depressed bipolar patients first exposed to antidepressant monotherapy had higher switch rates and more suicide attempts than those treated with antidepressant/mood stabilizer combinations.

4.2 Antidepressants and Cycle Acceleration

Similarly, there has been concern expressed that antidepressants can accelerate episode frequency or induce rapid cycling in bipolar patients (Licht et al. 2008). This was reported in several case series (Kukopulos et al. 1980; Yildiz and Sachs 2003; Wehr and Goodwin 1979; Azorin et al. 2008). In a prospective longitudinal study, Bauer et al. (2005) compared the frequency and pattern of mood changes between BD patients treated with antidepressants or not. They found that those treated with antidepressants were depressed on twice as many days as those not so treated (29.0% compared with 14.8%). As part of the STEP-BD study, Ghaemi et al. (2010) randomized BP patients recovering from an acute depressive episode to continuing or not continuing antidepressant treatment. They found that a previous rapid cycling course predicted over three times more depressive recurrences with continued antidepressant treatment per year.

4.3 Antidepressants and Suicidal Behaviors

In 2007, the black box warning for antidepressants included recommendations that all persons initiating antidepressant therapy should be monitored closely for the possible development of suicidal ideation and behaviors. At this time, evidence that antidepressants may alter the risk of suicidal behavior in bipolar patients remains uncertain. Two retrospective studies (Yerevanian et al. 2007; Pacchiarotti et al. 2011a, b, c) found more suicidal behaviors in patients receiving antidepressants than in those receiving mood stabilizers with or without antidepressants. However, Leon et al. (2014) reported on a 27-year longitudinal study of antidepressant use in 206 subjects with BPI, 139 with BPII, and 361 with UP. In mixed-effect survival analyses, those with BPI had a significant reduction in risk of suicidal behavior by 54% (HR = 0.46; 95% CI, 0.31–0.69; $t = -3.74$; $P < 0.001$) during periods of antidepressant exposure compared to propensity-matched unexposed intervals. Similarly, the risk was reduced by 35% (HR = 0.65; 95% CI, 0.43–0.99; $t = -2.01$; $P = 0.045$) in BPII. Interestingly, there was no evidence of an increased or decreased risk with antidepressant exposure in unipolar disorder. Similarly, two prospective studies (Bauer et al. 2006; Tondo et al. 2008) of antidepressant use in BD depressed patients did not find evidence of altered risk for suicidal ideation or behaviors.

It should be noted that this association may be more likely to be seen in BD patients with mixed episodes. Three studies (Valentí et al. 2011; Pacchiarotti et al. 2011a, b, c; Baldessarini et al. 2012) have found an association of lifetime mixed episodes and higher rates of antidepressant use with increased risk of suicide behaviors.

5 Conclusions

Traditional antidepressant use in BD continues to be a source of controversy in psychiatry. Overall efficacy data has suggested that there may be a role for traditional antidepressant use in BD depressions but that the effect is not the robust response seen in studies of unipolar depression treatment. Further, the mediocre efficacy data must be weighed against the potential that traditional antidepressants may have for doing harm. Unfortunately, these decisions are being based upon a relative paucity of data compared with need. Given the amount of disability and suffering caused by depressive episodes in bipolar disorder, and the limited amount of placebo-controlled trials in acute bipolar depression (and the even more rare number of trials in longer-term treatment), is it any wonder that practicing psychiatrists are unsure of how to make use of antidepressants? Further, it is believed that the continued high use of traditional antidepressants may be due in part to the limited options, efficacy, and tolerability of other treatments (Fountoulakis 2010), or the need to treat comorbidities (such as anxiety disorders), or perhaps even pressure from patients themselves asking for relief from the symptoms of depression (Vieta 2014).

Even experts in the field struggle to find consensus. Parker et al. (2017) compared 11 expert consensus guidelines generated between 2002 and 2015. They noted that

while there was some consistency on key recommendations, there was also substantial inconsistencies, limiting the generation of any "meta-consensus" model for managing bipolar depression.

In 2013, the International Society of Bipolar Disorders (ISBD) convened a task force of identified experts to review the data and make recommendations on antidepressant use in BD (Pacchiarotti et al. 2013). Their published review noted the striking incongruity between the wide use of antidepressants in clinical practice and the weak evidence base for their efficacy and safety; yet that same limited database also limited the consensus of recommendations. The task force reached a consensus on only 12 statements about the use of antidepressants in bipolar disorder. These are listed in Table 3. Even then, some of the statements were felt to be open to debate. For example, Tundo et al. (2015) conducted a 12-week, open-label clinical trial of 255 mood disorder patients with depression (154 UP, 49 BPI, 52 BPII) treating them using the ISBD guidelines for 12 weeks. They found response and remission rates did not differ significantly among the three groups.

Table 3 Recommendations from the ISBD task force on antidepressant use in bipolar disorder

Acute depression treatment
1. Adjunctive antidepressants may be used for an acute bipolar I or II depressive episode when there is a history of previous positive response to antidepressants
2. Adjunctive antidepressants should be avoided for an acute bipolar I or II depressive episode with two or more concomitant core manic symptoms in the presence of psychomotor agitation or rapid cycling
Maintenance treatment
3. Maintenance treatment with adjunctive antidepressants may be considered if a patient relapses into a depressive episode after stopping antidepressant therapy
Monotherapy
4. Antidepressant monotherapy should be avoided in bipolar I disorder
5. Antidepressant monotherapy should be avoided in bipolar I and II depression with two or more concomitant core manic symptoms
Mood switching
6. Bipolar patients starting antidepressants should be closely monitored for signs of hypomania or mania and increased psychomotor agitation, in which case antidepressants should be discontinued
7. The use of antidepressants should be discouraged if there is a history of past mania, hypomania, or mixed episodes emerging during antidepressant treatment
8. Antidepressant use should be avoided in bipolar patients with a high mood instability (i.e., a high number of episodes) or with a history of rapid cycling
Mixed states
9. Antidepressants should be avoided during manic and depressive episodes with mixed features
10. Antidepressants should be avoided in bipolar patients with predominantly mixed states
11. Previously prescribed antidepressants should be discontinued in patients currently experiencing mixed states
Drug class
12. Adjunctive treatment with norepinephrine-serotonin reuptake inhibitors or tri- and tetracyclics should be considered only after other antidepressants have been tried and should be closely monitored because of an increased risk of mood switch or destabilization

Interestingly, the dropout rate was significantly higher for patients with UP (18.2%) than for patients with BPI (2%) and BPII (7.7%) disorder. When antidepressant safety was reviewed, one patient with BPI depression had a suicide attempt, and antidepressant-emerging mood switch was observed in 2.9% of patients of bipolar patients. The authors concluded that the ISBD guidelines were effective, though they recommended partially modifying ISBD Recommendations 1 and 4, to include potential responders and to improve safety. Obviously, recommendations for antidepressant use in bipolar disorder will continue to require further revisions and clarification in the future as more research allows.

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