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The use of antidepressants for bipolar disorder - a controversy between science and clinical practice

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Depressive episodes are in many ways more challenging for patients and clinicians than other bipolar disorder episodes, including manic or mixed mood episodes: 1. the prevalence of depressive episodes is higher than those of manic or mixed episodes [1, 2], 2. psychosocial functioning is more impaired [3, 4], 3. cognitive function is more impaired [5], 4. suicide is more prevalent [6] and finally, 5. treatment is more complex in depressive episodes [7].

Use of antidepressants in bipolar disorder in clinical practice

Antidepressants are frequently used for bipolar disorder in clinical practice. In Denmark, 88% of patients with a first discharge diagnosis of mania or bipolar disorder from a psychiatric hospital received antidepressants during the 1995–2005 period [8], and 40–60% received them within one year after diagnosis [9]. Similarly, in a European drug surveillance programme covering the 1994-2009 period, 74% received antidepressants [10]. In a more recent review from 2024 comprising patients with bipolar disorder from North America, Europe and Australia, antidepressants were prescribed cross-sectionally for 38%, being among the most prescribed medications [11]. It should be noted that although antidepressants may be used for bipolar depression, many patients with bipolar disorder have concurrent comorbid anxiety or obsessive–compulsive disorders for which antidepressants may also be effective.

Aims of THIS paper

This paper aims to highlight the controversy between the poor evidence from science on the effects of antidepressants for bipolar depression and the high use of antidepressants in clinical practice - and further point to alternative drugs for treatment of bipolar depression. The paper summarises: 1) findings from a recent systematic review and network meta-analysis on comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults published by Yildiz et al in Lancet Psychiatry 2023 [7], 2) the risk of switching to mania associated with the use of antidepressants for bipolar depression and 3) the pharmacological recommendations for treatment of bipolar depression by the “Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD)”, 2018, [12] 4) the use of electroconvulsive therapy (ECT) for bipolar depression and 5) arguments for giving priority to drugs that have a proven effects in all phases of bipolar disorder. Based on a summary of these findings, pharmacological

recommendations for treating bipolar depression are provided, outlining the clinical role of antidepressants in bipolar disorder.

1. Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults

The comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults were recently investigated in a well-conducted systematic review and network meta-analysis published by Yildiz et al [7], comprising 101 randomised controlled trials covering 20,081 study participants and 68 medications and placebo. No single drug was identified to have been investigated in randomised controlled trials (RCTs) with high confidence in the evidence.

Comparative efficacy and tolerability of antidepressants for acute bipolar depression in adults

In the above-mentioned systematic review and network meta-analysis [7], antidepressants seemed to be an efficacious drug class but were associated with a higher risk for manic switch than antipsychotics [7]. **Table 1** presents standard mean differences (SMD (95% confidence interval (CI)) for eight different antidepressants versus placebo based on 20 identified RCTs comparing an antidepressant drug with placebo, according to Yildiz et al. [7].

TABLE 1 Standard mean differences (SMD) (95% CI) between antidepressant drugs and placebo according to a systematic review and network meta-analysis published by Yildiz et al. [7].

Antidepressant drug	RCTs/patients, n	SMD (95%CI)
Venlafaxine	3/157	0.47 (0.11-0.83)
Sertraline	2/103	0.43 (–0.06-0.93)
Imipramine	3/141	0.30 (–0.03-0.63)
Paroxetine	4/189	0.18 (–0.06-0.42
Bupropion	3/78	0.17 (–0.35-0.69)
Citalopram	3/71	0.08 (–0.32-0.48)
Agomelatine	1/168	–0.02 (–0.30-0.34)
Moclobemide	1/81	–0.04 (–0.57-0.49)

As shown in the "Number of trials" and "Number of patients" columns in the table, antidepressants were overall poorly investigated in small RCTs and with low to moderate SMDs between drug and placebo (SMD (95% CI). Among the published RCTs, many were negative trials. An example of a relatively large RCT is a study on citalopram versus placebo [13] (that, for unclear reasons, was not included in the paper by Yildiz et al [7]). The study included 119 subjects with bipolar disorder, type I or type II acute depressive episodes, who were randomised to citalopram or placebo in addition to standard mood stabilisers. Follow-up was six weeks for acute efficacy (primary outcome) and up to a year for maintenance efficacy (secondary outcome). The study was powered for a clinically meaningful effect size. Citalopram in combination with standard mood stabilisers had

no clinical benefits compared with placebo for either acute or maintenance treatment of bipolar depression. Maintenance treatment led to worsened manic symptoms, especially in patients with a rapid-cycling course [13].

The findings on antidepressants by Yildiz et al [7] are in line with a prior systematic review and meta-analysis from 2016 focusing on randomised, double-blind, placebo-controlled trials of second-generation antidepressants adjunctive to a mood stabiliser or an antipsychotic in patients with acute bipolar depression [14]. It was concluded that "adjunctive second-generation antidepressants are associated with reduced symptoms of acute bipolar depression, but the magnitude of benefit is small because they do not increase clinical response or remission rates". It was further concluded that "these medications should be used only in the short term because prolonged use is associated with an increased risk of treatment-emergent mania or hypomania". A recent 2024 meta-analysis of 18 RCTs corroborated these findings for antidepressants in general; it similarly reported small effects corresponding to a 12% absolute increase in response (number needed to treat (NNT) ≈9) and an SMD of –0.20 versus placebo for adjunctive antidepressants [15]. These figures are within the same range as those for some antidepressants in unipolar depression. Finally, the effects of adjunctive antidepressants during the maintenance phase of bipolar disorder have rarely been investigated. Although a meta-analysis from 2017 suggested beneficial effects [16], a recent large RCT found no significant benefits of adjunctive continuation of escitalopram or bupropion XL for 52 weeks compared with treatment for eight weeks in terms of preventing relapse of any mood episode [17].

According to Yildiz et al. [7], lithium monotherapy, with low to very low evidence confidence, was more efficacious than placebo in reducing depressive symptoms, based on four studies including 298 patients (SMD: 0.18 (-0.06-0.42).

Antiepileptics in monotherapy according to Yildiz al. [7]

Lamotrigene: At least six negative trials [18] out of 11 RCTs (N = 948), with *moderate* confidence in the evidence, but with a small effect size (SMD: 0.16 (0.03-0.29).

Divalproate: Six small placebo-controlled studies, N = 162, with *low or very low* confidence in the evidence (SMD: 0.51 (0.15-0.97)

Atypical antipsychotics in monotherapy

With *moderate* confidence in the evidence, four atypical antipsychotics were found efficacious in reducing depressive symptoms according to Yildiz al. [7]: Quetiapine (300-600 mg day): Seven out of seven studies positive, N = 2,152, SDM: 0.35 (0.23-0.47), Olanzapine: four RCTs, N = 732 (SDM: 0.35 (0.17-0.54), Lurasidone: Four RCTs, N = 1,029, SDM: 0.29 (0.14-0.45) and Cariprazine: Four RCTs, N = 997, SDM: 0.23 (0.06-0.39). Furthermore, two atypical antipsychotics have not been shown to have any effect. Aripiprazole: Two RCTs, including 186 and 187 patients, respectively, with bipolar I depression found no effect of aripiprazole versus placebo during eight weeks [19]. Similarly, two RCTs including 298 patients [20, 21] with an unclearly defined number of patients with bipolar I depression (>190) [21] found no effect of Ziprasidone versus placebo for six weeks.

2. Mania associated with antidepressant treatment

A comprehensive meta-analytic review study from 2010 investigated the risk of mania–hypomania in bipolar disorder and major depressive disorder (MDD) in 35 RCTs and open trials of patients with versus without exposure to antidepressant drugs (ADs) [22]. The overall risk of mania with/without antidepressants averaged 12.57.5%. Antidepressant-associated mania was more frequent in bipolar disorder than in MDD patients. Furthermore, tricyclic antidepressants were riskier than selective serotonin-reuptake inhibitors (SSRIs). Mood stabilisers had minor effects, probably confounded by their preferential use in mania-prone patients [22]. It was

concluded that the use of ADs in adults with BPD or MDD was highly prevalent and moderately increased the risk of mania overall, with little protection being achieved from using mood stabilisers. Conversely, the most recent systematic review and network meta-analysis from 2025 by Oliva et al [23], including 13 RCTs and 1,362 patients with bipolar depression, concluded that: "although some evidence of increased risk of switching to mania was observed, no antidepressant was associated with a significantly higher risk of switch to mania compared to placebo. Venlafaxine showed the highest risk estimate among antidepressants, though no statistically significant relative risk (RR) (4.53 (95% CI 0.47–43.25)), and was the only compound with consistent signals of increased switch in individual studies". It should be noted that patients who have *previously* responded to and tolerated antidepressants are rarely included in RCTs (where prior or current antidepressant use is usually an exclusion criterion), influencing the generalisability of results from placebo-controlled trials.

Furthermore, a recent systematic review on triggers of acute mood episodes in bipolar disorder [24] including a total of 108 studies (case reports/case series, interventional, prospective and retrospective studies) concluded that while several decompensation triggers were identified, pharmacotherapy was the one with the largest body of evidence, particularly the use of antidepressants as triggers of manic/hypomanic episodes. Other identified triggers for mania were brain stimulation, including ECT/transcranial magnetic stimulation (TMS), energy drinks, acetyl-l-carnitine, St. John's wort, seasonal changes, hormonal changes and viral infections.

Evidence that antidepressant treatment in bipolar depression can precipitate manic or hypomanic episodes is corroborated by Frye et al. (2009) [25], who reported that patients with even minimal manic symptoms at baseline (Young Mania Rating Scale score ≤5) were at increased risk of treatment-emergent mania. Furthermore, potential predictors of affective switching with antidepressants may include bipolar I disorder (versus bipolar II), mixed features during depression, tricyclics and partly dual-action inhibitors versus modern antidepressants [26], rapid cycling and possibly a history of drug abuse, especially stimulant abuse [27]. According to findings from the National Institute of Mental Health's Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), two-thirds of patients with bipolar I or II depressive syndromes have concomitant manic symptoms, typically distractibility, flight of ideas or racing thoughts and psychomotor agitation [28]. Together, findings from these two studies [25, 28] may suggest that antidepressants should generally not be used in two-thirds of patients with bipolar depression who present with subtly increased psychomotor tempo, pressured speech and racing thoughts. Notably, manic symptoms often accompany bipolar depressive episodes but may easily be overlooked as they may appear less prominent than the depressive features [28]. Conversely, findings from national register-based studies suggest that the risk of mania may not be increased when antidepressants are combined with a mood stabiliser [29, 30]. As concluded by Oliva et al [23], "antidepressants remain a treatment option for acute bipolar depression, particularly as add-on therapy. Their use should be individualised, considering patient-specific profiles and other potential risks, in line with a precision psychiatry approach. Further studies are needed to clarify long-term safety".

Comorbid anxiety and obsessive-compulsive disorder

The lifetime prevalence of any anxiety disorder in bipolar disorder is around 45% [31]. SSRIs or venlafaxine (with a mood stabiliser) remain first-line treatment for panic, generalised anxiety disorder (GAD) and social anxiety; for such conditions, an SSRI or aripiprazole augmentation may be considered after mood stabilisation.

3. Recommended first-line choices in the guideline from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD),

The most recent authoritative international guideline for the management of patients with bipolar disorder by the CANMAT and the ISBD (2018) [12] recommends the following first-line drugs for bipolar depression: quetiapine, lithium, lamotrigine and lurasidone. Antidepressants are not recommended, although the combined

tablet olanzapine-fluoxetine (Symbyax), which is not available in Denmark, is recommended as a second-line treatment for bipolar depression [12]. Finally, long-term treatment for bipolar disorder is strongly recommended, but guidelines do not recommend the use of antidepressants as a maintenance treatment [12, 32].

4. Response to electroconvulsive therapy in bipolar depression

The effect of electroconvulsive therapy (ECT) on bipolar depression has not been investigated in RCTs, and the maintenance effect is controversial, with potential side effects including cognitive effects. Nevertheless, in observational studies, ECT seems to have response rates in the 65-80% range and remission rates of 55-65%, slightly lower than for unipolar depression [33]. In a Swedish register-based study including 1,251 patients with bipolar depression, a response was achieved in 80% according to Clinical Global Impression scores [34]. Older age was associated with a higher ECT response rate, whereas patients with comorbid obsessive-compulsive disorder or personality disorder and patients previously treated with lamotrigine had a lower response rate [34].

5. Priority to drugs that have proven effects in all phases of bipolar disorder

Treatment of bipolar disorder comprises treatment of the acute mood states and prevention of relapse or recurrence during the maintenance phase. Bipolar depression is one of the three mood states in bipolar disorder, also comprising (hypo-)mania and mixed episodes. Thus, it is clinically recommended to give priority to drugs that have proven effects in all phases of bipolar disorder [35]. The optimal mood stabiliser has effects in acute mania, mixed episodes and bipolar depression and prevents relapse/recurrence of mania, mixed episodes and depression [36]. Lithium is the drug that most qualifies to fulfil the term a mood stabiliser with a proven effect in mania, possibly bipolar depression [7], and prevention of manic as well as depressive episodes [35-38]. Specifically, the evidence base for the maintenance effect of lithium in bipolar disorder is far stronger than for any other drug [12, 39-41], comprising at least 21 RCTs comparing lithium with other drugs or placebo [39] in addition to a total study base of 71 studies (N = 30,542) [41]. Nevertheless, guidelines still rank lithium among several other first-line options.

Finally, psychotherapy, including cognitive behavioural therapy and interpersonal and social rhythm therapy, may be used as non-pharmacological adjuncts.

Summary

Pharmacological recommendations for the treatment of bipolar depression in clinical practice:

- Always consider maintenance treatment.

- Use lithium as the basic treatment, specifically for bipolar disorder type 1, and combine with:

- Quetiapine (best evidence), depending on the patient's risk of cardiovascular disease and metabolic risk profile, use the following alternatives: lurasidone, cariprazine

- Lamotrigine may be considered when lithium or antipsychotics are unsuitable; the expected effect size is small and the onset is slow

- Avoid antidepressants in bipolar depression presenting with subtle increased psychomotor tempo, pressured speech and racing thoughts due to the increased risk of switch and potentially rapid cycling

- Consider ETC as a viable option for the treatment of bipolar depression resistant to pharmacological treatment

- Never treat with antidepressants without a mood stabiliser

- If an antidepressant is added, use mainly SSRIs due to their low switch rate

- If an antidepressant is used in maintenance treatment, the occurrence of manic/mixed symptoms should be monitored carefully

The above recommendation is consistent with current Danish guidelines for the pharmacological treatment of bipolar disorder [42], which recommend lithium, quetiapine and lamotrigine as first-line agents for bipolar I disorder, current depressive episode, in at least 70% of patients, and for bipolar II disorder, current depressive episode, in at least 60%. Guidelines are currently updated by the Danish Health Authority, Denmark

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ABSTRACT

Depressive episodes are more challenging for patients and clinicians than other bipolar disorder episodes. The reasons for this include: 1. the prevalence of depressive episodes is higher than for other episodes; 2. functioning; 3. cognition is more impaired; 4. suicide is more prevalent; 5. and treatment is more complex. This paper aims to highlight the controversy between the poor evidence from science on the effects of antidepressants for bipolar depression versus the high use of antidepressants in clinical practice, and to specify the clinical role of antidepressants in bipolar disorder in relation to other drugs.

KEY POINTS

Recommendations for the treatment of bipolar depression:

- Always take maintenance treatment into account.
- Use lithium as a basic treatment
- Consider an atypical antipsychotic
- Alternatively consider lamotrigene
- Avoid antidepressants in bipolar depression presenting with subtle agitation.
- Consider electroconvulsive therapy
- If an antidepressant is added, use mainly selective serotonin-reuptake inhibitors owing to the low switch rate.

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