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Bipolar depression: a review of treatment options

Kate Levenberg, Zachary A Cordner

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Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Correspondence to
Dr Zachary A Cordner; zac@jhmi.edu

ABSTRACT

Bipolar depression (BD-D) is both common and incredibly challenging to treat. Even treated individuals with BD-D experience depression approximately 19% of the time, and subsyndromal depression an additional 18%. This stands in clear contrast to the approximately 10% of time spent in hypomania and 1% of time spent in mania. Despite this high illness burden, there remain relatively few treatment options approved by the US Food and Drug Administration for BD-D. Of the approved medications, four are second-generation antipsychotics (SGAs) and one is an SGA combined with an antidepressant. However, particularly when used long-term, antipsychotics can pose a significant risk of adverse effects, raising the clinical conundrum of weighing the risks associated with long-term antipsychotic use versus the risk of relapse when patients are off medications. Here, we review commonly used treatments for BD-D, including antipsychotics, classic mood stabilisers, electroconvulsive therapy and psychotherapy. We then address the somewhat controversial topic of antidepressant use in BD-D. Finally, we summarise emerging treatment options and highlight ongoing clinical trials. We hope this review will help compare the risks and benefits of several common and novel options for the treatment of patients with BD-D. In doing so, we also hope this review will aid the individualised selection of treatments based on each patient's history and treatment goals.

INTRODUCTION

Treatment of bipolar depression (BD-D) continues to represent a significant unmet need.[1 2] On average, patients with bipolar disorder (both bipolar I (BD-I), defined by the presence of mania, and bipolar II (BD-II), defined by presence of hypomania) who are treated according to established guidelines are euthymic only about 50% of the time.[3] Further, patients with bipolar disorder spend three times more days depressed than manic or hypomanic. Depression, therefore, represents a quite common mood state among patients with bipolar disorder.[3] This is particularly worrisome as BD-D significantly impacts an individual's psychosocial functioning, with impairments in work, social and family life.[3] Suicides, which are disproportionately high in bipolar disorder, predominantly occur in the depressive state.[3] Furthermore, BD-D is the major contributor to disability associated with the illness.[3]

Despite these serious adverse impacts of bipolar disorder, over 50% of patients with bipolar disorder are at least partially non-adherent to medications.[4] Many factors contribute to non-adherence, including lack of psychoeducation and insight into the chronic and episodic nature of the disease.[4] Additionally, a significant number of patients experience intolerable side effects of medications. Studies examining patient narratives found that fears of side effects are a common reason for non-adherence.[4]

Given the enormous burden of BD-D, the development of effective treatment options represents an urgent priority. To date, the US Food and Drug Administration (FDA) has approved several drugs for the treatment of BD-D, including a combination of olanzapine plus fluoxetine (OFC) (approved 2003), quetiapine (2008), lurasidone (2013), cariprazine (2019) and lumateperone (2021) (table 1).[2 5] Although effective in clinical trials, these treatment options are often practically limited by intolerability and adverse effects, particularly for long-term maintenance use, raising the clinical conundrum of weighing the risks associated with long-term antipsychotic use versus the risk of relapsing when patients are off medications. Here, we review the evidence for and adverse effects of currently approved treatment options. We then review several commonly used 'off label' strategies and summarise the ongoing controversy surrounding antidepressant use in BD-D. Finally, we discuss emerging treatment options and briefly highlight several groundbreaking research initiatives that may eventually shed light on novel treatment approaches.

FDA-APPROVED MEDICATIONS FOR TREATMENT OF BD-D

Olanzapine and fluoxetine (approved in 2003)

OFC was the first drug approved by the US FDA to specifically treat BD-D.[6] In a

Table 1 Summary of FDA-approved medications for bipolar depression

Pharmacological agent	Year approved	Common adverse effects	Effectiveness
Olanzapine + fluoxetine	2003	► Weight gain ► Nausea ► Diarrhoea ► Diabetes ► Dyslipidaemia ► Cardiovascular disease	► OFC therapy significantly reduced the severity of depressive symptoms when compared with a placebo (OR: 0.38, 95% CI: 0.24 to 0.59). ► OFC therapy also reduced relapse rate (NNT=5).
Quetiapine	2008	► Sedation ► Extrapyramidal symptoms ► Dizziness ► Fatigue ► Constipation ► Weight gain	► Quetiapine significantly decreased Clinical Global Impression-Severity scores or Clinical Global Impression for Bipolar Severity of Illness scores (mean difference=−4.66, 95% CI: −5.59 to −3.73).
Lurasidone	2013	► Akathisia ► Somnolence ► Extrapyramidal symptoms	► Lurasidone is described as having similar efficacy in mitigating depressive symptoms with similar overall effect sizes compared with OFC and quetiapine.
Cariprazine	2019	► Insomnia ► Extrapyramidal symptoms ► Nausea ► Sedation ► Dizziness ► Constipation	► Cariprazine is associated with a small but significant reduction in depression symptoms, as assessed by the MADRS (standard mean difference: −0.26, 95% CI: −0.49 to −0.02).
Lumateperone	2021	► Sedation ► Nausea ► Dizziness ► Dry mouth	► Lumateperone had significantly greater MADRS response rate (51.1% vs 36.7%; OR=2.98, p<0.001) and remission rate (p=0.02) compared with placebo.

CI, confidence interval; FDA, Food and Drug Administration; MADRS, Montgomery-Asberg Depression Rating Scale; NNT, needed to treat; OFC, olanzapine plus fluoxetine; OR, odds ratio.

meta-analysis of four randomised controlled trials (RCT) (1330 patients), OFC therapy significantly reduced the severity of depressive symptoms when compared with a placebo (odds ratio (OR): 0.38, 95% confidence interval (CI): 0.24 to 0.59), olanzapine (OR: 0.56, 95% CI: 0.36 to 0.86) and lamotrigine (OR: 0.70, 95% CI: 0.49 to 0.99).[6] OFC therapy also reduced relapse rate, with a number needed to treat (NNT) of 5.[6] However, OFC was not associated with a significant difference in level of depression or mean change in suicidal thoughts.[6]

It is important to note that, in these clinical trials, OFC was associated with more frequent and more severe adverse effects compared with all alternatives, except when compared with olanzapine monotherapy. Adverse effects of OFC therapy are similar to those of olanzapine, but also include higher rates of nausea and diarrhoea.[7] The number needed to harm (NNH) for OFC treatment for all adverse effects, excluding weight gain, is 17 (95% CI: 9 to 97). The NNH specifically for clinically significant weight gain is 5 (95% CI: 4 to 7).[6] When comparing the ratio of NNH with NNT, a calculation to illustrate trade-offs between benefits (response) and harms (adverse effects), OFC reaches about 1 when weight gain is included as a harm.[8] In the long term, olanzapine, like other second-generation antipsychotics (SGAs), has been associated with metabolic syndrome, including weight gain, diabetes, dyslipidaemia and cardiovascular disease.[9] Additionally, although the mechanisms of the association remain unclear, olanzapine and other SGAs have been linked to increased all-cause mortality.[10]

Related, at least in part, to these high rates of adverse effects, olanzapine use is also complicated by high discontinuation rates. In a study comparing antipsychotic medications, nearly 50% of patients were at least partially non-adherent to all antipsychotics, and olanzapine had among the lowest adherence rates .[11] In this study, only slightly more than one-third of patients continued to take olanzapine as prescribed for a 270-day period.[11]

Quetiapine (approved in 2008)

In a meta-analysis of 11 RCTs (n=3488), quetiapine significantly decreased the Clinical Global Impression-Severity scores or Clinical Global Impression for Bipolar Severity of Illness scores (mean difference=−4.66, 95% CI:

−5.59 to −3.73).[12] Quetiapine also appears to have positive effects on anxiety, sleep quality and overall functioning, while decreasing risk of mania.[12] Common adverse effects include sedation, extrapyramidal symptoms (EPS), somnolence, dizziness, fatigue, constipation, dry mouth, increased appetite and weight gain.[12] Prominent sedation occurs in most patients, and quetiapine is commonly prescribed for insomnia.[13] The NNH for clinically significant weight gain is 16.[7] When compared with placebo, other significant adverse effects include dry mouth (42.5% for quetiapine vs 11.1% for placebo, NNH=4), dizziness (16.8% vs 8.0%, NNH=12), constipation (9.9% vs 4.5%, NNH=19), extrapyramidal syndrome (8.6% vs 3.3%, NNH=19) and fatigue (9.6% vs 6.0%, NNH=28).[7]

Lurasidone (approved in 2013)

In 2013, the FDA approved the use of lurasidone to treat BD-D, either as monotherapy or as adjunctive treatment with lithium or valproate.[14] In a meta-analysis of 12 systematic reviews, lurasidone is described as having similar efficacy in mitigating depressive symptoms with similar overall effect sizes compared with OFC and quetiapine.[15] Lurasidone causes less weight gain than OFC and less sedation than quetiapine.[15] The most frequent adverse effects with the largest difference in incidence versus placebo are nausea, akathisia and somnolence.[8] EPS and dystonia are also relatively common.[15] The NNT for response in a 6-week multi-study RCT was 5, while the NNH to the degree that results in discontinuation was 642.[8]

Cariprazine (approved in 2019)

Cariprazine is also approved with a specific indication for BD-D. A meta-analysis and review revealed that cariprazine is associated with a small but significant reduction in depression symptoms, as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS) (standard mean difference: −0.26, 95% CI: −0.49 to −0.02).[16] Commonly encountered adverse effects include insomnia, EPS, akathisia, sedation, nausea, dizziness and constipation.[17] Increases in weight are relatively small compared with other antipsychotics, although significantly higher than placebo.[18] Adverse effects appear to be more severe at higher dosages and overall the NNH in BD-D is 20.[16]

Lumateperone (approved in 2021)

Lumateperone was recently approved as monotherapy or adjunctive therapy with lithium or valproate for treatment of depression in the context of either BD-I or BD-II disorder.[19] Lumateperone is unique in that it modulates serotonin, dopamine and glutamate simultaneously.[5] In a study of 377 patients, lumateperone had significantly greater MADRS response rate (51.1% vs 36.7%; OR=2.98, p<0.001) and remission rate (p=0.02) at day 43 compared with placebo.[5] Participants in this study reported good tolerability of lumateperone with relatively low risk of EPS, metabolic changes and prolactin elevation.[5] In the most recent clinical trial, mean changes from baseline in weight, fasting glucose, total cholesterol, triglycerides and low-density cholesterol were similar between lumateperone and placebo.[19] The most common adverse effects include sedation, nausea, dizziness and dry mouth.[19]

OTHER COMMON TREATMENTS FOR BD-D

The US FDA approval process relies on a review of manufacturer-provided information regarding safety and effectiveness of a drug for specific indications. Once approved for a specific indication, 'off label' use is allowed. There are several drugs not approved by the FDA that are commonly used 'off label' for treatment of BD-D and have substantial supporting evidence.

Classic mood stabilisers

Lithium is effective in the acute treatment of mania and long-term maintenance of mood and prophylaxis,[20] and may be particularly effective in a subset of patients. There are few trials comparing lithium with placebo for BD-D, but a small study of 29 patients with acute depression assigned to lithium or imipramine after a placebo trial found a 32% reduction in depressive symptoms among patients treated with lithium for 4 weeks.[21] Despite clear evidence of long-term benefits, including robust antisuicidal effects,[22] the evidence for rapid or short-term benefits of lithium in acute BD-D is generally considered modest.[20]

Of the antiepileptic mood stabilisers, lamotrigine, which has been found to have antidepressant effects in placebo-controlled trials,[7] may be best supported. In a meta-analysis of five RCTs (n=1072), lamotrigine improved MADRS, with a relative risk (RR) of 1.22 (95% CI: 1.06 to 1.41, p=0.005). The author concludes that the overall pool effect was modest, although the advantage over placebo was larger in patients with more severe depression.[7] Some evidence also exists for use of carbamazepine and oxcarbazepine as secondary choices.[2] In a meta-analysis of monotherapy (including lamotrigine, carbamazepine and valproic acid), mood stabilisers are moderately efficacious for acute BD-D (RR=1.30, 95% CI: 1.16 to 1.44; NNT=10, 95% CI: 7 to 18), but studies are few and limited by the high rates of discontinuation.[23]

Regarding risks, lithium has a narrow therapeutic range, and approximately half of patients within the therapeutic range will experience side effects that are rated moderate to severe intensity.[24] Adverse effects of lithium include excessive thirst, polyuria, weight gain, tremor, nausea, diarrhoea and memory disturbances.[24] Emotional and cognitive blunting and sexual dysfunction are also commonly experienced.[25] Renal impairment can occur and can be severe, especially with supratherapeutic levels.[26] Especially long-term use is associated with thyroid dysfunction,[27] with approximately 20% of patients eventually developing hypothyroidism and 9% experiencing hyperparathyroidism.[28] Antiepileptics including lamotrigine, valproate and carbamazepine are associated

with sedation, somnolence, distractibility, insomnia and dizziness.[27] Antiepileptics also commonly cause sexual dysfunction and significant weight gain.[29] Uncommon but serious adverse reactions to antiepileptic mood stabilisers include Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anaemia and hepatotoxicity.[30]

Other antipsychotics

Other SGAs that have at least some supporting evidence but no FDA approval for treatment of BD-D include asenapine, risperidone, clozapine, aripiprazole and ziprasidone.[29–37] Asenapine has been shown to be particularly effective in mixed episodes, as shown by two RCTs with a subgroup of 173 patients experiencing mixed states.[31] In a 12-week RCT with 30 patients, risperidone and risperidone plus paroxetine were equally but modestly effective when added to a mood stabiliser for BD-D.[34] In a retrospective study of 326 patients, adjunctive clozapine therapy lowered the number of hospitalisations associated with BD-D, as well as the number of days in the hospital.[33] In meta-analyses, aripiprazole significantly reduced depressive symptoms early in treatment, but the results were not significantly different from placebo at 8 weeks.[35] However, a post-hoc analysis suggests aripiprazole may be more effective in patients with severe depression, particularly at a lower dose.[35] Further, aripiprazole may be particularly useful in patients with comorbid obsessive-compulsive disorder (OCD).[36] In an open trial of 30 patients with depression in the context of BD-II, 60% of those treated with ziprasidone responded to treatment by the end of 8 weeks of treatment.[32] Other studies have found no significant antidepressant effect of ziprasidone when used in the context of BD-I.[37]

These, like the SGAs approved for treatment of BD-D, often cause metabolic syndrome, including weight gain, diabetes, dyslipidaemia and cardiovascular disease.[9] Other common side effects include hypotension, sedation, anticholinergic symptoms, hyperprolactinaemia, EPS, electrocardiographic changes and sexual dysfunction.[27] Less common but serious side effects include tardive dyskinesia, neuroleptic malignant syndrome, seizures, agranulocytosis, hypersensitivity reactions and an increased risk of mortality from all causes, especially in older adult patients with dementia-related psychosis.[38] Although generally similar, the side effect profiles of these SGAs do vary. For example, compared with other SGAs, asenapine poses relatively less risk of parkinsonism, dystonia and anticholinergic effects but relatively more weight gain and glucose abnormalities.[39] Risperidone poses a higher risk of hyperprolactinaemia but relatively fewer anticholinergic side effects.[40] Clozapine carries a higher risk of weight gain, glucose abnormalities, hyperlipidaemia, anticholinergic side effects, sedation, agranulocytosis and electrocardiographic abnormalities, including QT interval prolongation.[41] Finally, aripiprazole causes relatively less weight gain but relatively more akathisia.[42]

First-generation antipsychotics (FGAs) are less often used in BD-D due to side effects, including EPS and tardive dyskinesia.[43] Haloperidol, which has emerged as the most commonly used FGA, has a narrow therapeutic window and results in EPS in 20%–30% of patients.[43] Like SGAs, FGAs are also associated with increased all-cause mortality.[44]

Electroconvulsive therapy

Electroconvulsive therapy (ECT) provides a rapid clinical response and can therefore be used in urgent clinical situations, including, for example, the presence of suicidal behaviour, severe psychosis or catatonia.[45] On average, patients with BD-D experience clear benefit after seven ECT treatments,[46] although the range in the number of treatments needed varies widely. A recent RCT of 73 patients with treatment-resistant BD-D compared the efficacy of pharmacological treatment versus ECT and found that 74% of the ECT group showed significant response versus only 35% for those receiving pharmacological treatment; however, both groups had similar rates of remission of around 30%.[47] Regarding adverse effects, memory impairment is common during the course of treatment, although temporary in most cases.[48] Other common side effects include temporary headache, muscle pain and anaesthesia-associated nausea.[49] More severe but rare side effects include bone and soft tissue injury, prolonged seizure and induction of mania.[49]

Cognitive–behavioural therapy

Psychotherapy is well accepted with a relatively low risk of adverse effects.[50] In a review of the adverse effects of cognitive-behavioural therapy (CBT) for bipolar disorder, psychotherapy was associated with initial increased anxiety but then increased well-being later on.[51] In a meta-analysis of 19 RCTs (n=1384), CBT lowered the relapse rate of BD-D (OR=0.506, 95% CI: 0.278 to 0.921) and improved depressive symptoms when measured across several rating scales (g=−0.494, 95% CI: −90.963 to −0.026).[52] Subgroup analyses indicate that longer CBT sessions, particularly those lasting >90 min, have a lower relapse rate.[52]

CONTROVERSY SURROUNDING ANTIDEPRESSANT USE

In the treatment of BD-D, conventional wisdom is to avoid antidepressants or use them as second-line treatment due to the risk of inducing mania.[6] However, many patients with bipolar disorder are prescribed antidepressants in practice,[53] not all antidepressants carry the same risk of conversion to mania, and it is increasingly clear that a subset of patients benefits greatly from treatment with antidepressants. Regarding the risk of inducing mania, a meta-analysis including data from 1088 patients found that the switch rate for tricyclic antidepressants was 10% and for all other antidepressants combined, it was 3.2%.[54] In the same meta-analysis, 4.7% of placebo-treated patients switched, and there was no overall significant difference in switch rates between antidepressants and placebo.[54] Two studies have found that venlafaxine is associated with a higher risk of short-term switches, but

it is unclear if other serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine also pose a higher risk.[55] Long-term antidepressant use does seem to clearly increase the risk of mood episodes among individuals with rapid cycling bipolar disorder. A study of 68 patients with depression with known rapid cycling found that continuation of antidepressants in addition to a mood stabiliser beyond the acute depressive episode resulted in 268% more total mood episodes per year compared with subjects without rapid cycling on the same treatment.[56] Patients with rapid cycling treated with antidepressants that were discontinued after the initial response did not experience an increase in total mood episodes per year.[56]

In terms of the efficacy of antidepressants in BD-D, several reviews and meta-analyses have come to differing conclusions, likely reflecting differences in statistical techniques and inclusion criteria[55] and pointing towards a need for further investigation. Two of the most recent meta-analyses found no significant benefit of adding antidepressants to mood stabilisers for the treatment of BD-D.[57 58] In agreement with these findings, the STEP-BD trial, which included 4360 patients, found that adding antidepressants to mood stabilisers did not result in better clinical outcomes than those achieved with mood stabilisers alone.[59] In contrast, naturalistic studies suggest that there is likely a sizeable subgroup of patients who respond to a mood stabiliser plus an antidepressant with no increase in switching.[55] Interestingly, there is more consistent evidence of benefits when antidepressants are added to SGAs.[55] Whether this reflects additive effects of antidepressants combined specifically with SGAs or some other factors is unknown. A separate meta-analysis comparing different antidepressants found no significant difference in rates of clinical response between antidepressants, but it did report lower switch rates for bupropion when compared with sertraline, venlafaxine and desipramine.[60] Importantly, the analysis concluded that the results are significantly limited by lack of high-quality studies.[60]

The risk of conversion to mania or induction of mood cycling has, by far, received the most attention, while far less is said about the overall tolerability of antidepressants in BD-D. Importantly, antidepressants have a rather favourable side effect profile. In a meta-analysis of antidepressants in BD-D, patients in the placebo arm dropped out of the study due to side effects more often than in the antidepressant arm (49% vs 32%, respectively).[54] Other reports state that the side effects of antidepressants are mild, and often patients experience none.[61] Common side effects of selective serotonin reuptake inhibitors (SSRIs) include insomnia, dry mouth, nausea, diarrhoea, headaches, weight gain and sexual side effects.[61] The side effect profile of bupropion includes headache, dry mouth, nausea, insomnia and very rarely seizure, but lower rates of sexual dysfunction, weight gain and somnolence.[62] The NNH is between 20 and 90 for SSRIs[63] and between 15 and 20 for bupropion.[64] The rates for discontinuation due to side effects for bupropion in the treatment of BD-D or major depressive disorder (MDD) range from 5% to 11%,[65] 27% for SSRIs and 30% for tricyclic antidepressants (TCAs).[66]

In a summary of the available meta-analyses on this topic, Gitlin[55] offered the following conclusions, which would seem to remain sound advice:

> 1. The efficacy of antidepressants in bipolar depression remains unproven; 2. When added to mood stabilisers, antidepressants are not associated with increased switch (treatment emergent affective switch, TEAS); 3. No consistent evidence has demonstrated cycle acceleration in bipolar disorder on modern antidepressants (especially with mood stabiliser co-treatment); 4. Bipolar II patients may be safely treated (at least in the short term) with antidepressants; 5. A subset of bipolar patients, both bipolar I and II, will need a maintenance regimen of mood stabilizers plus antidepressants and will not show mood instability with this regimen.[55]

EMERGING TREATMENT OPTIONS

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is thought to be safe and potentially effective in BD-D, but the approach has been less well studied in BD-D than MDD.[67] In a review of 14 studies (n=274), response rates (defined as a 50% reduction in symptoms compared with baseline) were significantly higher in repetitive TMS (rTMS) compared with sham treatment (OR=2.72, 95% CI: 1.44 to 5.14).[68] When different stimulation protocols were analysed, response was seen for high-frequency rTMS over the left dorsolateral prefrontal cortex (OR=2.57, 95% CI: 1.17 to 5.66).[68] Additionally, deep TMS may be particularly effective for BD-D.[69] Overall, although common side effects are few and mild,[70] and early results for BD-D are promising, additional RCTs are needed to firmly conclude that rTMS should be offered routinely for BD-D.

Ketamine

Esketamine, the S (+) enantiomer of ketamine, was approved by the FDA for treatment-resistant unipolar depression in 2019.[71] Data on ketamine or esketamine for treatment of BD-D are limited but growing, and it has been suggested for treatment-resistant depression in both BD-I and BD-II.[72 73] In a meta-analysis of 14 RCTs in which patients received ketamine (n=234) or a non-ketamine N-methyl-D-aspartate receptor (NMDAR) antagonist (n=354), ketamine initially reduced BD-D symptoms compared with placebo but lost its superiority by days 10–12.[74] A separate review of 10 studies (n=167) agreed with these findings of significant benefit lasting up to 1 week.[75] Ketamine is often regarded as safe, with most adverse effects, including the common feelings of dissociation, abating within 2 hours.[76] However, little data exist on the psychiatric use of ketamine in patients with medical comorbidities,[76] and there is a need for larger

RCTs exploring long-term outcomes. Currently, there is at least one National Institutes of Health (NIH)-funded clinical trial exploring ketamine for BD-D.

Vagal nerve stimulation

Vagal nerve stimulation has been approved by the FDA for treatment-refractory unipolar depression.[77] In a recent 5-year prospective study, 63% of patients with treatment-resistant BD-D treated with adjunctive vagal nerve stimulation therapy had a significant reduction in depressive symptoms as measured by a 50% or greater reduction in the MADRS, compared with 39% of patients receiving treatment-as-usual.[78] Further, vagal nerve stimulation was associated with a significantly greater mean reduction in suicidality in one study.[78] Common side effects of vagal nerve stimulation include cough, hoarseness, voice alteration and paraesthesia.[79]

Thyroid supplementation

Thyroid supplementation is a well-established strategy for treating unipolar depression.[80] In a review of T3 supplementation for patients with BD-D (n=353), T3 was found to augment and accelerate treatment response to antidepressants and lithium, as well as protect against relapse during the first few years of treatment.[81] In a review of eight clinical trials (n=78), supplementation with supraphysiological doses of T4 had antidepressant effects in up to 50% of patients with depression (unipolar and bipolar).[82] T4 supplementation in BD-D appears to be well tolerated, with little evidence of cardiovascular side effects.[4] In a study comparing the adverse effects of T3 in BD-D, 16% of patients discontinued treatment due to side effects, the most common being tremor.[83]

Pramipexole

In a review of five RCTs, three open-label trials and five observational studies (n=505) in patients with either unipolar or bipolar depression, pramipexole was associated with a remission rate of 39.6%, which was a superior response rate to placebo (RR=1.77, 95% CI: 1.11 to 2.82) and similar to SSRIs (RR=0.93, 95% CI: 0.44 to 1.95).[84] In a study adding pramipexole to a mood stabiliser for BD-D, the mean percentage of improvement from baseline Hamilton Depression Scale scores was greater for patients taking pramipexole (48%) than for those taking placebo (21%).[85] Common adverse effects of pramipexole include tremor, restlessness, ataxia and nausea.[86] Risk of mood cycling as a result of pramipexole should be further evaluated.[86]

N-acetylcysteine

In a meta-analysis of six clinical trials (n=248), augmentation with the antioxidant N-acetylcysteine (NAC) for BD-D appears to be superior to placebo, with a moderate effect size, but a large CI (d=0.45, 95% CI: 0.06 to 0.84).[87] Adverse effects of NAC were comparable with placebo, but included dyspepsia, diarrhoea, vomiting, headache and dizziness.[87] In an RCT investigating adjunctive treatment with NAC and aspirin, participants with NAC plus aspirin experienced a 17% reduction in depressive symptoms compared with placebo after 16 weeks of treatment.[88]

ONGOING AND RECENTLY COMPLETED CLINICAL TRIALS

Perhaps further highlighting the need for additional treatment options, there are several ongoing clinical trials for BD-D. The following list is not exhaustive but is intended to give a sense of the breadth of mechanisms of action that are being considered potentially useful in BD-D. The list of clinical trials is presented in an order that reflects the phase of clinical trials, from recruitment to completed phase III trials.

Light therapy, which is well established as treatment for seasonal affective disorder, is currently being studied for use in BD-D, and the trial is in the recruitment phase (NCT00590265). Tai chi and qigong are both being studied for subsyndromal BD-D in older adults, and the trial is in the recruitment phase (NCT04450147). Vestibular stimulation, which has been shown to be an effective non-invasive treatment for major depression, is being studied for BD-D and is in the recruitment phase (NCT02778256). In a related manner, scopolamine is in phase II of an RCT (NCT04211961). Also in phase II trials are adjunctive oral uridine (NCT00841269), the antiglucocorticoid mifepristone (NCT0043654), and felbamate, an anticonvulsant that is FDA-approved for partial and generalised seizures (NCT00034229). An atypical antipsychotic, bifeprunox, is in a phase III clinical trial (NCT00134459).

MANAGING ADVERSE EFFECTS

A number of strategies have been developed to help manage adverse effects associated with the treatment options available. Lifestyle interventions, such as exercise and dietary changes, may be important to mitigate weight gain and may also positively impact residual mood symptoms.[89] Some have suggested that, in some cases, weight gain can be addressed pharmacologically with topiramate,[90] metformin or betahistine.[91] In patients experiencing akathisia in the setting of antipsychotic medication use, several strategies have been proposed, including cautious dose reduction, cross-tapering or the addition of propranolol or benztropine.[92] Other EPS, such as parkinsonism, should similarly be addressed by first considering dose reduction or switching to a different pharmacological agent before considering the addition of other agents like benztropine.[93] The effects of sedation, a common side effect across several drug classes, can often be at least partially managed by consolidating medications at nighttime. Stimulants, which are sometimes used to counter cognitive side effects and cognitive symptoms of depression, are controversial in the context of BD-D as they may increase the risk of switch to hypomanic, manic or mixed states.[94]

Managing the adverse effects of lithium has been well studied. In fact, many issues with intolerability can be

avoided by slow titration and providing reassurance that many patients experience reduction in side effects over time.[24] Renal and thyroid effects should be monitored regularly. If hypothyroidism develops, treatment with levothyroxine is indicated.[24] For patients who develop polyuria, maintaining adequate hydration is essential. Additionally, there is some evidence that diuretics may be helpful, although fluid balance, renal function and electrolyte levels should be monitored closely.[24] For lithium-associated nausea, lithium should be taken with food or after meals, and a sustained release formulation may be helpful.

DISCUSSION

As prudently stated by Cohen,[2] 'Medications that do not work on average may help some patients, and medications that do work on average will not be appropriate for all patients. Individual cases require thoughtful trials of the alternatives tailored to each person'.[2] This may be especially important in BD-D, which is a particularly difficult state to treat. Clinical decision making for this disorder may be best thought of on a case-by-case basis.

Additionally, prospective data are needed to further inform the long-term risk versus benefit trade-offs of atypical antipsychotics in BD-D. While the FDA-approved medications do clearly impact the severity of depressive episodes, long-term use of antipsychotics has significant adverse effects; they are often discontinued due to intolerability, and when continued as maintenance therapy, there is little guidance as very few studies have looked beyond the acute phase of treatment in BD-D. In a recent study that did attempt to assess the value of mood stabilisers, antipsychotics and antiepileptics during the maintenance phase, the following medications outperformed placebo: aripiprazole plus valproate, lamotrigine, lamotrigine plus valproate, lithium, olanzapine, and quetiapine.[95] However, it is important to consider that trials examining antipsychotics versus placebo are sparse, and more studies are required to allow more reliable clinically definitive outcomes.[15] Similarly, head-to-head comparisons between treatments for BD-D are limited.[96] As such, there have been efforts to compare treatments for BD-D, but these efforts are significantly limited.

Many have called for renewed consideration of antidepressants when used in combination with mood-stabilising medications, and recent review articles on the acute use of antidepressants in BD-D highlight a compelling need for further studies with longer follow-up periods and careful definition of emerging mania.[54 55] Others have suggested that, while the risk of mania induction with antidepressants exists, it may have historically been overestimated.[6] Further, 'proneness' towards pharmacologically induced mania via antidepressant use may occur in a clinical subpopulation,[97] suggesting that others may be at relatively lower risk. It is thus reasonable to conceptualise antidepressant risk and likely therapeutic benefit as complex and multideterminant phenomena. Factors that one might consider in this debate are history of antidepressant-induced mania, bipolar subtype, existence of rapid cycling, recency of last manic episode, comorbid substance use, antidepressant class and choice of concurrent mood stabiliser.[97]

There are several 'off-label' medications strongly supported by evidence and commonly used by providers and patients, including, but not limited to, lithium, lamotrigine, carbamazepine, oxcarbazepine and valproic acid. ECT and CBT also have considerable evidence supporting their common use. There are also many options currently in development, such as TMS, ketamine, vagal nerve stimulation, thyroid supplementation, pramipexole and NAC, as well as several ongoing clinical trials.

Individual treatment plans should carefully weigh out risks and adverse effects and tailor treatment based on the suspected best tolerated side effects. Additionally, it is thought that there are certain subpopulations or 'pheno-biotypes' within bipolar disorder that may respond better to certain treatments.[98] For example, it is well known that within bipolar disorder, patients may be categorised as 'lithium responders' or 'non-lithium responders'.[99] While a review is beyond the scope of this article, an increasing number of groups are researching personalised medicine approaches to predict which treatments patients will respond best to. This often includes genetic sequencing, brain imaging or machine learning prediction.[100] Significant development of these approaches may help in determining appropriate initial treatment choices and may also help identify which patients are at the highest risk of adverse effects of certain treatments.

CONCLUSION

Despite adequate treatment according to current guidelines, many patients with bipolar disorder experience frequent depressive symptoms and spend significantly more time depressed than manic or hypomanic.[3] For this reason, both the acute treatment of BD-D and the maintenance therapy between mood episodes often fail to fully address patients' needs. The current FDA-approved medications for BD-D include OFC, quetiapine, lurasidone, cariprazine and lumateperone, all of which come with clearly established short-term benefits but also significant long-term adverse effects. It is thus imperative to both investigate the long-term risk–benefit trade-offs and explore novel treatment approaches. Encouragingly, there are already several alternative options in wide use, such as classic mood stabilisers, ECT and antidepressants. Additionally, there are several promising clinical trials ongoing, as summarised above. We hope this review may aid clinicians in selecting suitable, individualized treatment for patients with BD-D and emphasise the importance of weighing specific adverse effects.

PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES (PRISMA) GUIDELINES AND SEARCH CRITERIA

The current study relied on a scoping review approach. The current study is not intended as a comprehensive or systematic review of the literature. Therefore, the current study was not registered with international prospective register of systematic reviews (PROSPERO).

All articles included in this review were accessed using PubMed, the Harrell Health Sciences Library or the NIH ClinicalTrails.gov database. This review considered for inclusion studies that were published at the time of the database search, printed in English and related to adult bipolar disorder.

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ORCID iD

Zachary A Cordner http://orcid.org/0000-0001-6000-567X

REFERENCES

1 Kupka RW, Altshuler LL, Nolen WA, *et al*. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord* 2007;9:531–5.
2 Cohen BM. Evidence-Based drug treatment of acute depression in bipolar disorder. *JAMA Psychiatry* 2019;76:1314–5.
3 Miller S, Dell'Osso B, Ketter TA. The prevalence and burden of bipolar depression. *J Affect Disord* 2014;169 Suppl 1:S3–11.
4 Chakrabarti S. Treatment-adherence in bipolar disorder: a patient-centred approach. *World J Psychiatry* 2016;6:399–409.
5 D'Souza I, Durgam S, Satlin A, *et al*. Lumateperone (ITI–007) in the treatment of bipolar depression: results from a randomized clinical trial. *CNS Spectr* 2021;26:150.
6 Silva MT, Zimmermann IR, Galvao TF, *et al*. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. *J Affect Disord* 2013;146:310–8.
7 Shen Y-C. Treatment of acute bipolar depression. *Tzu Chi Med J* 2018;30:141–7.
8 Citrome L, Ketter TA, Cucchiaro J, *et al*. Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord* 2014;155:20–7.
9 Roerig JL, Steffen KJ, Mitchell JE. Atypical antipsychotic-induced weight gain: insights into mechanisms of action. *CNS Drugs* 2011;25:1035–59.
10 Ralph SJ, Espinet AJ. Increased all-cause mortality by antipsychotic drugs: updated review and meta-analysis in dementia and general mental health care. *J Alzheimers Dis Rep* 2018;2:1–26.
11 Sajatovic M, Valenstein M, Blow FC, *et al*. Treatment adherence with antipsychotic medications in bipolar disorder. *Bipolar Disord* 2006;8:232–41.
12 Suttajit S, Srisurapanont M, Maneeton N, *et al*. Quetiapine for acute bipolar depression: a systematic review and meta-analysis. *Drug Des Devel Ther* 2014;8:827–38.
13 Anderson SL, Vande Griend JP. Quetiapine for insomnia: a review of the literature. *Am J Health Syst Pharm* 2014;71:394–402.
14 Bawa R, Scarff JR. Lurasidone: a new treatment option for bipolar depression-a review. *Innov Clin Neurosci* 2015;12:21–3.
15 Fornaro M, De Berardis D, Perna G. Lurasidone in the treatment of bipolar depression: systematic review of systematic reviews. *Biomed Res Int* 2017;2017:e3084859.
16 Pinto JV, Saraf G, Vigo D, *et al*. Cariprazine in the treatment of bipolar disorder: a systematic review and meta-analysis. *Bipolar Disord* 2020;22:360–71.
17 Citrome L. Cariprazine: chemistry, pharmacodynamics, pharmacokinetics, and metabolism, clinical efficacy, safety, and tolerability. *Expert Opin Drug Metab Toxicol* 2013;9:193–206.
18 Earley W, Durgam S, Lu K, *et al*. Safety and tolerability of cariprazine in patients with acute exacerbation of schizophrenia: a pooled analysis of four phase II/III randomized, double-blind, placebo-controlled studies. *Int Clin Psychopharmacol* 2017;32:319–28.
19 Antrim A. FDA approves lumateperone for the treatment of bipolar depression, 2021. Available: https://www.pharmacytimes.com/view/fda-approves-lumateperone-for-the-treatment-of-bipolar-depression [Accessed 28 Dec 2021].
20 Malhi GS, Tanious M, Das P, *et al*. Potential mechanisms of action of lithium in bipolar disorder. Current understanding. *CNS Drugs* 2013;27:135–53.
21 Fieve RR, Platman SR, Plutchik RR. The use of lithium in affective disorders. I. Acute endogenous depression. *Am J Psychiatry* 1968;125:487–91.
22 Sarai SK, Mekala HM, Lippmann S. Lithium suicide prevention: a brief review and reminder. *Innov Clin Neurosci* 2018;15:30–2.
23 Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. *Br J Psychiatry* 2010;196:266–73.
24 Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord* 2016;4:27.
25 Licht RW. Lithium: still a major option in the management of bipolar disorder. *CNS Neurosci Ther* 2012;18:219–26.
26 Aiff H, Attman P-O, Aurell M, *et al*. Effects of 10 to 30 years of lithium treatment on kidney function. *J Psychopharmacol* 2015;29:608–14.
27 Dols A, Sienaert P, van Gerven H, *et al*. The prevalence and management of side effects of lithium and anticonvulsants as mood stabilizers in bipolar disorder from a clinical perspective: a review. *Int Clin Psychopharmacol* 2013;28:287–96.
28 Murru A, Popovic D, Pacchiarotti I, *et al*. Management of adverse effects of mood stabilizers. *Curr Psychiatry Rep* 2015;17:603.
29 Kaufman KR, Coluccio M, Sivaraaman K, *et al*. Lamotrigine-Induced sexual dysfunction and non-adherence: case analysis with literature review. *BJPsych Open* 2017;3:249–53.
30 Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet Neurol* 2012;11:792–802.
31 Azorin JM, Sapin C, Weiller E. Effect of asenapine on manic and depressive symptoms in bipolar I patients with mixed episodes: results from post hoc analyses. *J Affect Disord* 2013;145:62–9.
32 Liebowitz MR, Salmán E, Mech A, *et al*. Ziprasidone monotherapy in bipolar II depression: an open trial. *J Affect Disord* 2009;118:205–8.
33 Nielsen J, Kane JM, Correll CU. Real-World effectiveness of clozapine in patients with bipolar disorder: results from a 2-year mirror-image study. *Bipolar Disord* 2012;14:863–9.
34 Shelton RC, Stahl SM. Risperidone and paroxetine given singly and in combination for bipolar depression. *J Clin Psychiatry* 2004;65:1715–9.
35 Yatham LN. A clinical review of aripiprazole in bipolar depression and maintenance therapy of bipolar disorder. *J Affect Disord* 2011;128 Suppl (1):S21–8.
36 Amerio A, Odone A. Aripiprazole augmentation in treating comorbid bipolar disorder and obsessive-compulsive disorder. *Gen Psychiatr* 2018;31:e100007.
37 Lombardo I, Sachs G, Kolluri S, *et al*. Two 6-week, randomized, double-blind, placebo-controlled studies of ziprasidone in outpatients with bipolar I depression: did baseline characteristics impact trial outcome? *J Clin Psychopharmacol* 2012;32:470–8.
38 Kheirbek RE, Fokar A, Little JT, *et al*. Association between antipsychotics and all-cause mortality among community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2019;74:1916–21.
39 Musselman M, Faden J, Citrome L. Asenapine: an atypical antipsychotic with atypical formulations. *Ther Adv Psychopharmacol* 2021;11:20451253211035269.
40 Stojkovic M, Radmanovic B, Jovanovic M, *et al*. Risperidone induced hyperprolactinemia: from basic to clinical studies. *Front Psychiatry* 2022;13:874705.

41 De Berardis D, Rapini G, Olivieri L, *et al*. Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine. *Ther Adv Drug Saf* 2018;9:237–56.
42 Rapagnani MP. Safety, efficacy, and patient acceptability of aripiprazole in the maintenance treatment of bipolar disorder. *Clinical Medicine Insights: Therapeutics* 2012;4:131–44.
43 Dibben CRM, Khandaker GM, Underwood BR, *et al*. First-generation antipsychotics: not gone but forgotten. *BJPsych Bull* 2016;40:93–6.
44 Murray-Thomas T, Jones ME, Patel D. Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. *Cardiovasc Psychiatry Neurol* 2013;2013:247486.
45 Perugi G, Medda P, Toni C, *et al*. The role of electroconvulsive therapy (ECT) in bipolar disorder: effectiveness in 522 patients with bipolar depression, mixed-state, mania and catatonic features. *Curr Neuropharmacol* 2017;15:359–71.
46 Popiolek K, Bejerot S, Brus O, *et al*. Electroconvulsive therapy in bipolar depression - effectiveness and prognostic factors. *Acta Psychiatr Scand* 2019;140:196–204.
47 Perugi G, Quaranta G, Belletti S, *et al*. General medical conditions in 347 bipolar disorder patients: clinical correlates of metabolic and autoimmune-allergic diseases. *J Affect Disord* 2015;170:95–103.
48 Akambadiyar R, Bhat PS, Prakash J. Study of memory changes after electroconvulsive therapy. *Ind Psychiatry J* 2018;27:201–5.
49 Andrade C, Arumugham SS, Thirthalli J. Adverse effects of electroconvulsive therapy. *Psychiatr Clin North Am* 2016;39:513–30.
50 Linden M, Schermuly-Haupt M-L, Definition S-HML. Definition, assessment and rate of psychotherapy side effects. *World Psychiatry* 2014;13:306–9.
51 Gonzalez-Pinto A, Gonzalez C, Enjuto S, *et al*. Psychoeducation and cognitive-behavioral therapy in bipolar disorder: an update. *Acta Psychiatr Scand* 2004;109:83–90.
52 Chiang K-J, Tsai J-C, Liu D, *et al*. Efficacy of cognitive-behavioral therapy in patients with bipolar disorder: a meta-analysis of randomized controlled trials. *PLoS One* 2017;12:e0176849.
53 Pacchiarotti I, Bond DJ, Baldessarini RJ, *et al*. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry* 2013;170:1249–62.
54 Gijsman HJ, Geddes JR, Rendell JM, *et al*. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 2004;161:1537–47.
55 Gitlin MJ. Antidepressants in bipolar depression: an enduring controversy. *Int J Bipolar Disord* 2018;6:25.
56 El-Mallakh RS, Vöhringer PA, Ostacher MM, *et al*. Antidepressants worsen rapid-cycling course in bipolar depression: a STEP-BD randomized clinical trial. *J Affect Disord* 2015;184:318–21.
57 McGirr A, Vöhringer PA, Ghaemi SN, *et al*. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *Lancet Psychiatry* 2016;3:1138–46.
58 Sidor MM, MacQueen GM. An update on antidepressant use in bipolar depression. *Curr Psychiatry Rep* 2012;14:696–704.
59 Bowden CL, Perlis RH, Thase ME, *et al*. Aims and results of the NIMH systematic treatment enhancement program for bipolar disorder (STEP-BD). *CNS Neurosci Ther* 2012;18:243–9.
60 Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry* 2011;72:156–67.
61 Ramic E, Prasko S, Gavran L, *et al*. Assessment of the antidepressant side effects occurrence in patients treated in primary care. *Mater Sociomed* 2020;32:131–4.
62 Fava M, Rush AJ, Thase ME, *et al*. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry* 2005;7:106–13.
63 Arroll B, Elley CR, Fishman T. Antidepressants versus placebo for depression in primary care. *Cochrane Database Syst Rev* 2009;8:CD007954.
64 Magovern MK, Crawford-Faucher A. Extended-release bupropion for preventing seasonal affective disorder in adults. *Am Fam Physician* 2017;95:10–11.
65 Patel K, Allen S, Haque MN, *et al*. Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant. *Ther Adv Psychopharmacol* 2016;6:99–144.
66 Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* 1995;310:1433–8.
67 Garnaat SL, Yuan S, Wang H, *et al*. Updates on transcranial magnetic stimulation therapy for major depressive disorder. *Psychiatr Clin North Am* 2018;41:419–31.
68 Nguyen TD, Hieronymus F, Lorentzen R, *et al*. The efficacy of repetitive transcranial magnetic stimulation (rTMS) for bipolar depression: a systematic review and meta-analysis. *J Affect Disord* 2021;279:250–5.
69 Somani A, Kar SK. Efficacy of repetitive transcranial magnetic stimulation in treatment-resistant depression: the evidence thus far. *Gen Psychiatr* 2019;32:e100074.
70 Taylor R, Galvez V, Loo C. Transcranial magnetic stimulation (TMS) safety: a practical guide for psychiatrists. *Australas Psychiatry* 2018;26:189–92.
71 Correia-Melo FS, Leal GC, Carvalho MS, *et al*. Comparative study of esketamine and racemic ketamine in treatment-resistant depression: protocol for a non-inferiority clinical trial. *Medicine* 2018;97:e12414.
72 Skriptshak C, Reich A. Intranasal esketamine use in bipolar disorder: a case report. *Ment Health Clin* 2021;11:259–62.
73 Ramadan AM, Mansour IA. Could ketamine be the answer to treating treatment-resistant major depressive disorder? *Gen Psychiatr* 2020;33:e100227.
74 Kishimoto T, Chawla JM, Hagi K, *et al*. Single-dose infusion ketamine and non-ketamine N-methyl-D-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol Med* 2016;46:1459–72.
75 Wilkinson ST, Ballard ED, Bloch MH, *et al*. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry* 2018;175:150–8.
76 Włodarczyk A, Cubała WJ. Safety and tolerability of ketamine use in treatment-resistant bipolar depression patients with regard to central nervous system symptomatology: literature review and analysis. *Medicina* 2020;56:67.
77 Breit S, Kupferberg A, Rogler G, *et al*. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. *Front Psychiatry* 2018;9:44.
78 McAllister-Williams RH, Sousa S, Kumar A, *et al*. The effects of vagus nerve stimulation on the course and outcomes of patients with bipolar disorder in a treatment-resistant depressive episode: a 5-year prospective registry. *Int J Bipolar Disord* 2020;8:13.
79 Fisher B, DesMarteau JA, Koontz EH. Responsive vagus nerve stimulation for drug resistant epilepsy: a review of new features and practical guidance for advanced practice providers. *Front Neurol* 2021;11:610379.
80 Lampner C. Triiodothyronine in the treatment of bipolar depression. Available: https://www.psychiatryadvisor.com/home/depression-advisor/triiodothyronine-in-the-treatment-of-bipolar-depression/ [Accessed 28 Dec 2021].
81 Parmentier T, Sienaert P. The use of triiodothyronine (T3) in the treatment of bipolar depression: a review of the literature. *J Affect Disord* 2018;229:410–4.
82 Baumgartner A. Thyroxine and the treatment of affective disorders: an overview of the results of basic and clinical research. *Int J Neuropsychopharmacol* 2000;3:149–65.
83 Kelly T, Lieberman DZ. The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. *J Affect Disord* 2009;116:222–6.
84 Tundo A, de Filippis R, De Crescenzo F. Pramipexole in the treatment of unipolar and bipolar depression. A systematic review and meta-analysis. *Acta Psychiatr Scand* 2019;140:116–25.
85 Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 2004;161:564–6.
86 Dell'Osso B, Ketter TA. Assessing efficacy/effectiveness and safety/tolerability profiles of adjunctive pramipexole in bipolar depression: acute versus long-term data. *Int Clin Psychopharmacol* 2013;28:297–304.
87 Nery FG, Li W, DelBello MP, *et al*. N-acetylcysteine as an adjunctive treatment for bipolar depression: a systematic review and meta-analysis of randomized controlled trials. *Bipolar Disord* 2021;23:707–14.
88 Bauer IE, Green C, Colpo GD, *et al*. A double-blind, randomized, placebo-controlled study of aspirin and N-acetylcysteine as adjunctive treatments for bipolar depression. *J Clin Psychiatry* 2018;80:m12200.
89 Bauer IE, Gálvez JF, Hamilton JE, *et al*. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. *J Psychiatr Res* 2016;74:1–7.

90 Shivakumar V, Jayaram N, Rao NP, *et al*. Successful use of add - on topiramate for antipsychotic - induced weight gain. *Indian J Psychol Med* 2012;34:85–6.
91 Kang D, Jing Z, Li R, *et al*. Effect of betahistine and metformin on antipsychotic-induced weight gain: an analysis of two clinical trials. *Front Psychiatry* 2018;9:620.
92 Pringsheim T, Gardner D, Addington D, *et al*. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry* 2018;63:719–29.
93 D'Souza RS, Hooten WM. Extrapyramidal Symptoms. In: *StatPearls*. Treasure Island (FL: StatPearls Publishing, 2022.
94 Perugi G, Vannucchi G, Bedani F, *et al*. Use of stimulants in bipolar disorder. *Curr Psychiatry Rep* 2017;19:7.
95 Kishi T, Ikuta T, Matsuda Y, *et al*. Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials. *Mol Psychiatry* 2021;26:4146–57.
96 Johnsen E, Kroken RA. Drug treatment developments in schizophrenia and bipolar mania: latest evidence and clinical usefulness. *Ther Adv Chronic Dis* 2012;3:287–300.
97 Tundo A, Cavalieri P, Navari S, *et al*. Treating bipolar depression - antidepressants and alternatives: a critical review of the literature. *Acta Neuropsychiatr* 2011;23:94–105.
98 Rong C, Park C, Rosenblat JD, *et al*. Predictors of response to ketamine in treatment resistant major depressive disorder and bipolar disorder. *Int J Environ Res Public Health* 2018;15:771.
99 Alda M. Who are excellent lithium responders and why do they matter? *World Psychiatry* 2017;16:319–20.
100 Cordner ZA, MacKinnon DF, DePaulo JR. The care of patients with complex mood disorders. *Focus* 2020;18:129–38.

Kate Levenberg, MD, is currently a psychiatry resident at the John Hopkins University School of Medicine. Previously, she received her Bachelor of Arts in Public Health from Elon University with minors in art and biochemistry. She then completed medical training at the Penn State College of Medicine. Dr Levenberg is interested in the study and treatment of mood disorders. Her work specific to bipolar disorder has focused on identifying novel psychopharmacologic options, as well as integrating current data and theories into a model for pathophysiology. Additionally, Dr Levenberg is a certified yoga teacher and is passionate about holistic approaches to medicine.

Zachary A. Cordner, MD-PhD, is an Assistant Professor of Psychiatry & Behavioral Sciences at the Johns Hopkins University School of Medicine. He is also a faculty member of the Johns Hopkins Mood Disorders Center. Dr Cordner completed his medical training, PhD, psychiatry residency, and chief residency at Johns Hopkins. He was also named an Alexander Wilson Schweizer Fellow in Mood Disorders at Johns Hopkins. In addition to clinical expertise in complex and difficult to treat mood disorder, Dr Cordner conducts preclinical studies aiming to better understand the mechanisms of mood disorders and identify novel treatment options.