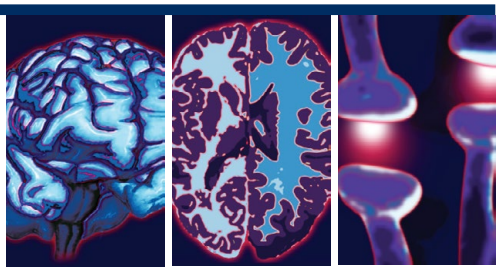
Review



Acute pharmacological treatment strategies for bipolar depression

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ABSTRACT

Besides maintaining long-term stability, the most difficult aspect in the management of bipolar affective disorder is the depressive phase. The similarities in the cluster of symptoms with unipolar depression, as well as factors related to the patient, psychiatrist and the treatment itself could make the tasks of diagnosing and treating bipolar depression extremely challenging. A lack of clear guidance makes the choice of medication even harder, especially with the presence of conflicting recommendations. In this review we will explore the evidence base for available medication options, from antidepressants, lithium, anticonvulsants and antipsychotics as well as from other groups. However, any conclusions and guidance still suffer from some degree of uncertainty due to the limitations of evidence for some drugs, especially the relative lack of head-to-head comparisons.

Keywords

Bipolar depression, Antidepressants, Mood stabilizers, Antipsychotics, Experimental treatments

Introduction

Bipolar affective disorder is a chronic disabling condition. While the acute presentation of mania does respond effectively to a wide range of medication, poor outcome and quality of life as well as impaired functionality is linked to the preponderant depressive morbidity and persistence of subsyndromal depressive symptoms [1,2].

Treatment of bipolar disorder in specialized centers should (and is able to) prioritize the longitudinal long-term outcome [3], as due to the length of referral processes patients are often either less symptomatic, or risks are under control due to their inpatient status. The practicing primary or secondary care clinician, however, who is confronted with a severely depressed bipolar patient, has to cope with a different issue: How to achieve some improvement in the short term to instill hope and control suicidal ideation? In these instances, the possibility of mood destabilization ranks second behind the apparent danger of suicide. As this article addresses primarily practicing clinicians who are not necessarily bipolar specialists, the focus is on how to manage the acute depressed episode which may last for months [4,5] and puts the patient on acute danger.

This article is meant to be educational and narrative, and does not constitute a systematic review and grading of evidence as there are several recent full reviews and meta-analyses available [6-10]. Instead of adding another systematic review we want to supply the reader with an overview of available options and general rules how to approach bipolar depression.

Diagnosing bipolar depression

Over diagnosing of Bipolar disorder may occur,

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especially in centers conducting and depending on commercial drug studies, or when diagnosis is based on patient self-assessment [11]. Underdiagnosing of bipolar depression, however, remains the more common problem, especially in not specialized settings with a lack of awareness and training in diagnosing Bipolar disorder, especially Bipolar II disorder [12]. The latter, in turn, may lead to a treatment plan that may be unfavorable for bipolar depressed patients. For this reason, some authorities and guidelines recommend besides a formal SCID interview [13] the use of validated self-assessment tools such as the Mood Disorder Questionaire (MDQ [14]), or the Hypomania Symptom Checklist-32 (HCL-32, [15]). However, it should be clear that those instruments are designed for screening, not for confirming a diagnosis, and the risk of overdiagnosing Bipolar disorder when giving them too much weight is apparent [11].

As per ICD and DSM the cross-sectional diagnostic criteria and symptomatic threshold of acute unipolar and bipolar depression are identical (MDE, major depressive episode). However, even without knowledge of previous manic or hypomanic episodes, one may argue that certain characteristics such as the age of onset and the family history can help in distinguishing one from the other [16]. Also other characteristics as itemized and rated in the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HDRS), namely inner tension, pessimistic thoughts, suicidal thoughts and fear, appear to be more predominant in bipolar compared to unipolar depression [17,18].

Nevertheless, despite these potential differences in cross-sectional symptom profiles, it is impossible to separate bipolar from unipolar depressive episode in an individual patient based on clear cut distinctions [19], therefore a proposed 'probabilistic 'approach might be required, to differentiate between the two in a patient with a major depressive episode and no clear prior manic, hypomanic or mixed episode. This was put forward by the International Society of Bipolar Disorder Guidelines Taskforce on Bipolar Depression, summarizing the so far available evidence [20] **(Table 1)**.

Achieving diagnostic certainty is crucial, as the similarity in the symptoms between bipolar and unipolar depression does not necessarily support the assumption that the same treatments which are effective in one should be equally effective in the other [17].

During the diagnostic assessment, it is important to rule out any reversible factor, which can contribute to depression and/or interfere with the treatment. Therefore, a full psychiatric and medical history is crucially important as well as screening for drug and alcohol abuse and identifying concurrent stressors [19].

Identifying risks and predictors of response

Before proceeding with considering management options, including different medication, it is important to assess safety and functioning, establish treatment setting and consider behavioral strategies as well as psych education [17,21].

The suicide lifetime rate in bipolar disorder has been estimated to be as high as about 13% in untreated and 5% in treated patients who have been hospitalized at least once [22]. The 2.5- fold relative risk reduction of suicide by treatment- in this study mostly antidepressants and/or lithium- point out the life-saving importance of appropriate treatment. The majority of suicides occur during depressed or mixed bipolar episodes, this need to be taken in consideration when thinking about the importance of managing this condition [19].

In bipolar depression, some available guidelines do recommend one intervention over another, but unlike mania, there is no uniformly consented established standard treatment for this condition, except quetiapine. Still the base of management is usually adequate psychotropic medication, though the challenge is to tailor this to the patient's need, ideally with complementary psychological intervention and/ or socio therapy [3,17,21]. Non-pharmacological treatments such as electroconvulsive treatment (ECT)/sleep deprivation and repetitive Trans cranial magnetic stimulation (rTMS) might be considered in selected patients [17].

When it comes to psychopharmacology, there are regularly particular circumstances which influence strongly the choice of treatment, and might predict the response to treatment [19]. These factors are in addition to the severity and the course of the illness. These are:

■ Patient related factors

- ✔ Previous response to treatment, although its value in predicting the outcome of the treatment has been rarely supported by evidence

- The presence of other co morbidities, whether psychiatric or physical, like anxiety disorders, personality traits (neurotic or maladaptive) and/or substance misuse, renal, hepatic or cardiovascular co morbidities.
- Disturbed sleep plays a crucial role not only in mania, but also in depression. Persistent sleep disturbance predict early relapse; on the other hand, true improvement of sleep quality is often a first sign of response to treatment [13].
- The patient's concordance is of exceptional importance. Sensitivity to side effects and illness perception play an equally important role.

■ Medication related factors

- Tolerability is important, so are the availability and the price of the medication.
- Potential risks from particular medications must be taken into consideration, such as short and intermediate term risks (e.g., toxicity in overdose, mood destabilization) as well as long term risks (e.g., metabolic syndrome)

■ Physician related factors

- Regular contact with the patient, at a weekly interval during the first month of treatment is strongly recommended, not only to assess the response to treatment but also to evaluate changes in the patient's psychopathological status. Special attention needs to be paid to suicidal ideation.
- When applicable, this also gives the physician the chance to check serum levels of certain medication for therapeutic drug monitoring [19].
- If the patient consents, relatives should be included and play an active part in the treatment plan.

A regular check of the accuracy of diagnosis, risks and treatment choice is standard of good quality care. **Table 2** supplies some audit recommendations, adapted from the 2016 British Association of Psychopharmacology Bipolar Guideline [3].

Table 1: A proposed 'probabilistic' approach to the diagnosis of bipolar I depression in a person experiencing a major depressive episode with no clear prior episodes of mania (adapted from [20]).

A likely BIPOLAR I DEPRESSION diagnosis should be considered if ≥ 5 of the following features are present*	**A likely UNIPOLAR DEPRESSION diagnosis should be considered if ≥ 4 of the following features are present***
Symptomatology	
Hypersomnia and/or increased daytime napping	Initial insomnia/reduced sleep
Hyperphagia and/or increased weight	Appetite and/or weight loss
Other 'atypical' depressive symptoms such as 'leaden paralysis'	
Psychomotor retardation	Normal or increased activity levels
Psychotic features and/or pathological guilt	Somatic complaints
Lability of mood/manic symptoms	
Course of illness	
Early onset of first depression (< 25 years)*	Later onset of first depression (> 25 years)*
Multiple prior episodes of depression (≥ 5 episodes)*	Long duration of current episode (> 6 months)*
Family history	
Positive family history of bipolar disorder	Negative family history of bipolar disorder
*Confirmation of the proposed numbers requires further study and consideration.	

Pharmacological treatment

Cave- Given the relative lack of evidence and supportive data about optimal treatment of bipolar depression, recommendations and guidelines might be vulnerable to be influenced by market strategies and opinion rather than evidence [24]. Therefore, the interested reader should not consult just one, but several up-to-date guidelines and form his own opinion. **Table 3** summarizes guidelines on bipolar depression that have been released since 2010.

There is still a considerable doubt about what treatment should be used in treating bipolar depression, and is a combination superior to monotherapy? A recent meta-analysis identified only 24 larger scale monotherapy trials of 10 different treatments for bipolar depression other than antidepressants that were considered to fulfill high methodological standards for inclusion: lamotrigine (5 trials), quetiapine (5), valproate (4), 2 each for aripiprazole, olanzapine, ziprasidone, and 1 each for carbamazepine, lithium, lurasidone, and olanzapine-fluoxetine. Overall, pooled drug-over-placebo responder-rate superiority (RR) was quite moderate (29% [CI: 19-40%]), and the number needed to treat (NNT) was 8.2 (CI: 6.4-11) [18]. We will discuss in the next section these medications and other options available, but will first have a look at the group of antidepressants.

Antidepressants

The neurochemistry and pathogenesis of bipolar disorder, especially the depressive phase, remain

Table 2: Audit recommendations in Bipolar patients (adapted and modified from [3]

DIAGNOSIS	RISKS AND PHYSICAL HEALTH
• Is there a structured patient-completed (or structured interview) record?	• Is suicide risk recorded?
• Is there a record of the manic symptoms in mania?	• Is neglect of self and dependents, exploitation by others considered?
• Is there a record of the depressive symptoms in depression?	• Is risk of violence or offending considered?
• Have symptoms of borderline personality disorder been recorded as present or absent?	• Is a physical health screen conducted annually? • Weight, blood pressure, lipids, fasting glucose • Renal and thyroid function, calcium concentration if taking lithium
• Is there a record of anxiety symptoms?	• Has appropriate treatment been offered for physical health problems?
• Has the history of alcohol and drug use (including caffeine) been documented?	
• Has impairment of memory and executive function (or functional impairment) been considered?	
MEDICATION	**MEDICATION (cont.)**
• **Lithium** • Has lithium been offered for maintenance treatment? • Is the use of lithium safe? (baseline EGFR, lithium concentrations, thyroid function, calcium) • Are serum concentrations of lithium measured regularly? • Are serum concentrations of lithium maintained above 0.6 and below 0.8meq/l?	• **Antidepressants** • Is prescription of antidepressants for depression or anxiety? • Is there evidence of treatment response to the antidepressant? • Is use justified? • Have options with a better evidence base for treating depression been considered (e.g., lamotrigine, quetiapine)
• **Dopamine antagonists/partial agonists** • Are doses within accepted limits? • Are multiple dopamine antagonists/ partial agonists being prescribed together? • Is long-term use justified?	• **Valproate** • Is valproate being used in women of childbearing age? • If so, is a written justification recorded in the case notes? • Has the patient clearly understood the risks? • Has effective contraception been offered?

poorly understood [19]. As mentioned above, depression is the more prolonged and prominent phase of bipolar disorder [20]. Conventional antidepressants, usually used for unipolar depression, such as the tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine re-uptake inhibitors (SNRI's), or bupropion were used traditionally to treat bipolar depression, despite that quite limited and inconsistent research has been carried out regarding their benefits and risks [21-27]. Early pilot trials and more recent placebo-controlled studies indicated that the TCA imipramine and the SSRI fluoxetine have some efficacy in treating bipolar depression [17,34].

Also, reversible and irreversible monoamine oxidase inhibitors (MAOIs) [35,36], as well as bupropion [37] seem to have similar or higher efficacy compared with imipramine or desipramine in treating bipolar depression; however, this statement is based on small studies without a placebo control.

Of the newer generation antidepressants, venlafaxine was found to have a role in treating bipolar II depression, with a low rate of treatment emergent mania [38,39], alluding that venlafaxine can be used as a monotherapy in bipolar II (not bipolar I) depression [40]. Venlafaxine seems to be better tolerated than paroxetine [41]; however, among the second generation antidepressants, venlafaxine may be associated with the highest risk of a switch to bipolar I mania [42,43].

Less is known about other newer antidepressants, e.g., mirtazapine or reboxetine, in the absence of large scale studies and limited data to assess their efficacy and risks of destabilizing the mood if used as a monotherapy [17]. Open data for add-on agomelatine looked promising [44], also in depressed Bipolar II patients [45]; however, a recently published proof of concept study has failed [46].

The lack of large randomized studies is to some degree compensated by several meta-analyses, two of them favoring the use of antidepressants in bipolar depression [28,30], one finding no advantage over placebo [29]. While acknowledging that the value of antidepressant use in bipolar depression is still controversial, and highlighting that the current evidence is not sufficient to inform clinical practice about the long term use of these medications, the meta-analysis by Vasquez et al, was able to confirm at least equal efficacy of antidepressants in bipolar depression compared to unipolar depression [30]. This finding has also been replicated in naturalistic studies by two independent groups [47,48].

The efficacy and safety of short term use of antidepressants in bipolar depression was previously also supported by a meta-analysis of evidence from randomized, controlled trials by Gijsman et al [28]. Antidepressants as a group were superior to placebo. Apart from TCA, antidepressants didn't differ from placebo in inducing treatment emergent affective switches (TEAS), though one of the limitations is that there was no systematic and identical approach

to examine for TEAS between studies [28,49]. The low rate of TEAS with antidepressants was also confirmed by the meta-analysis conducted by Sidor and McQueen (2011) [29]; however, the efficacy of antidepressants as a group was neither statistically significant nor clinically meaningful (NNT of 50).

Whereas the evidence for efficacy of antidepressants is not really based on high quality studies, but on meta-analyses and naturalistic cohort data, the assumption of a potential lack of efficacy of antidepressants in treating bipolar depression is supported by a large randomized placebo controlled trial with paroxetine [50], and another large placebo-controlled add-on study examining either paroxetine or bupropion [51], although especially the latter study has been criticized for methodological short-comings.

In the study by McElroy et al [50], 122 bipolar depressed patients received 20mg/d paroxetine in an 8-week trial designed primarily to test the efficacy of quetiapine. This makes this study the largest that, so far, examined an antidepressant monotherapy in bipolar depression. Quetiapine was found to be statistically superior to placebo, whereas paroxetine was not.

In the second study, Sachs et al (2007) [51] found no additional achievement in sustained remission of depressive symptoms by adding an antidepressant (paroxetine or bupropion) to already more or less clinically optimized treatment of BD patients with mood-stabilizing or antipsychotic drugs.

However, design issues such as dosing in the first and concomitant therapies in the second study do limit the interpretation of the results. **Table 4** summarizes the pivotal studies of antidepressants in acute bipolar depression.

In summary, it is not a surprise to have a discrepancy in recommendations based on the controversial findings and their interpretation. Consequently, most guidelines do not recommend antidepressants as monotherapy for acute or long-term treatment of bipolar depression. However, experts agree that a combination of antidepressant and an antimanic drug may be used for bipolar I or II acute depressive episode when there is a history of positive response to antidepressant(s) [31].

The impression about antidepressants being less effective might have been also influenced by their adverse effects, e.g., a potential worsening of agitation, anger and dysphoria as well as the fear of provoking TEAS, leading to uncertainty about appropriate dosing and duration of treatment [48,52].

Especially antidepressant– induced TEAS, possible cycle acceleration and increased suicide risk are under debate. Evidence so far suggests that the risk of TEAS is higher with TCA than with new generation antidepressants [53,54]. Among the second generation, the SNRI venlafaxine seems to have a higher risk of TEAS than SSRI [43]. Meta-analysis found that patients with bipolar I disorder had higher rates of TEAS than those with bipolar II disorder in both acute and maintenance trials, 14.3% versus 7.1%, and 23.4% versus 13.9%, respectively [55]. However, this finding might as well reflect the dynamics of the disease; a thorough analysis of risk factors for TEAS in the STEP-BD cohort [56] demonstrated that only patients with a history of suicide attempt, younger age at onset, and bipolar I subtype are on increased risk of TEAS when treated with antidepressants. Additional illness related factors as a history of a higher number of previous depressive episodes, current or lifetime rapid cycling and current substance use disorder also seem to increase the overall risk of affective switching, but independent from

Table 3: Selected recent guidelines (since 2010) in English containing recommendations for the treatment of bipolar depression.

Guideline	Method
World Federation of Biological Psychiatry 2010 [17]	Systematic literature search, ranking of evidence, recommendations based on evidence and expert consensus
Guideline for treatment of bipolar disorder by the Japanese Society of Mood Disorders, 2013 [134]	Literature reviewed by specialists (not clear whether selection is based on a systematic search), recommendations based on evidence and expert consensus
CANMAT/ISBD Update 2013[32]	Systematic literature search, ranking of evidence, recommendations based on evidence and expert consensus
National Institute of Clinical Excellence (NICE) 2014 [7]	Systematic literature search, ranking of evidence, recommendations based primarily on evidence, sometimes modified by consensus panel
Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder 2015 [70]	Systematic literature search, ranking of evidence, recommendations based on evidence and expert consensus, then reviewed by stakeholders and public
British Association of Psychopharmacology 2016 [3]	Based on the systematic literature search of NICE 2014 , additional search of evidence until 12/2015, ranking of evidence, recommendations based on evidence and expert consensus
The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017)[115]	Systematic literature search, ranking of evidence, recommendations based on evidence and expert consensus

Table 4: Summary of selected pivotal studies on antidepressant use in bipolar disorder that are, in part, discussed in this review. The table includes few placebo-controlled RCTs, but several randomized head to head comparisons that allow a rough estimate of the different potencies and safety profiles of antidepressants in bipolar depression.

Study	Number of Bipolar subjects	Comparators and doses	Duration	Efficacy parameters	Overall efficacy	Treatment-emergent mania	Remarks
Agosti & Steward 2007[135]	70 (all BPII)	Imipramine 250mg/d Phenelzine 65 mg/d Placebo	6 weeks	Percentage of responders (patients rated 1 or 2 on CGI-I)	IMI 56. 5 % Phenelzine 52 % Placebo 22,7 %	None	Post hoc analysis of [136], only patients with « atypical » depression
Amsterdam 1998 [38]	17 (all BPII)	Once versus twice daily venlafaxine, 37.5 to 225 mg/d	6 weeks	Change from baseline HAM-D score	Venlafaxine - 14	None	No placebo control
Amsterdam & Garcia-Espaňa 2000 [39]	15 (all BPII)	Once versus twice daily venlafaxine 37.5 to 225 mg/d	6 weeks	Reduction in HAM-D ≥50%	Venlafaxine: 63%	None	No placebo control; Post-hoc analysis of [38]
Calabrese et al 2007 [44]	21	Agomelatine 25 mg/d add on to lithium or valpromide	6 weeks	Response (50% improvement of baseline HAM-D 17 item score)	Agomelatine: 81 %	None during the 6 week acute trial (3 during a one year extension study)	Open label study, no placebo control
Cohn et al 1989[137]	89	Fluoxetine (20 to 80 mg/d) Imipramine (75 to 300 mg/d) Placebo	6 weeks	≥50% improvement on HAM-D after at least 3 weeks of study drug	Fluoxetine: 86% Imipramine: 57% Placebo: 38%	Fluoxetine: 0% Imipramine: 6.7% Placebo: 3.4%	Together with [102] most comprehensive evidence for fluoxetine in bipolar depression
Fogelson et al 1992[138]	11	Bupropion (mean maximum dose 286 mg; range 100–450 mg) add on to treatment	6 weeks	Response evaluated on the Global Assessment of Functioning (GAF) scale	Moderate-to-marked response: 7/11 patients (63.6%) No / minimal response: 4/11 patients (36.4%)	Bupropion: 55%	Open label study, no placebo control
Himmelhoch et al 1991[35]	56	Tranylcypromine 20–60 mg/d Imipramine 100–300 mg/d	6-week acute treatment + 10-week continuation	Response defined as CGI score of 2/3 sustained for at least 2 weeks	Tranylcypromine: 81% Imipramine: 48%	Tranylcypromine: 12% Imipramine: 24%	Study only in a subgroup: "anergic" bipolar depression, no placebo control
McElroy et al. 2010[50]	740; 122 with PAR	Paroxetine 20mg/d, Quetiapine 300 and 600 mg/d, Placebo	8 weeks	Change from baseline MADRS score	Paroxetine ; -13,76 Placebo : -12,60 No significant difference	No increase in switch rate: 10.7% with paroxetine 20 mg/d, and 8.9% with placebo	Largest monotherapy RCT of an antidepressant in Bipolar depression
Nemeroff et al 2001[76]	117 (35 with Paroxetine, 39 with imipramine)	Paroxetine (20–50 mg/d) Imipramine (50–300 mg/d) Placebo; all add-on to lithium	10 weeks	Response defined as HAM-D score ≤7 or CGI global improvement ≤2	Paroxetine: 45.5% Imipramine: 38.9% Placebo: 34.9% No significant difference to placebo for PAR and IMI	Paroxetine: 0% Imipramine: 7.7% Placebo: 2.3%	Post-Hoc analysis : Both paroxetine and imipramine were superior to placebo for patients with low serum lithium levels.
Post et al 2006[42]	174	Sertraline 50-200 mg/d Bupropion 75-450 mg/d Venlafaxine 37.5-375 mg/d; all add-on to ongoing mood stabilizers	10 weeks	Response defined as either a ≥50% improvement in IDS score, or a decrease in the CGI-BP depression score of ≥ 2 points	Bupropion 49% Sertraline 53% Venlafaxine 51%	Combined switch criterion of CGI-BP severity of mania ⩾3 or YMRS>13: Bupropion 14%, Sertraline 16% Venlafaxine 31%	RCT with no placebo control

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Study	Number of Bipolar subjects	Comparators and doses	Duration	Efficacy parameters	Overall efficacy	Treatment-emergent mania	Remarks
Sachs et al 1994[37]	19	Bupropion (358 ± 62 mg) Desipramine (140 ± 46 mg)	8 weeks plus 1-year follow-up	Response defined as 2 or more weeks during which HAM-D scores were improved by 50% from baseline	Bupropion: 63% Desipramine: 71%	Bupropion: 11% Desipramine: 50%	No placebo control
Sachs et al. 2007[51]	366 (179 on antidepressant + mood stabilizer)	Paroxetine (20–40 mg, mean dose 30 mg) or bupropion (150–300 mg, mean dose 300 mg) or Placebo added to a mood stabiliser	26 weeks	Durable recovery: At least eight consecutive weeks of euthymia (with no more than two depressive or two manic symptoms)	23% with antidepressants, 27,3% with placebo No significant difference	No increase in switch rate: 10.1 % with antidepressants, 10.7 % with placebo	Patients with break-through depression and multiple treatments including psychotherapy – little benefits of any treatment modality (durable recovery rates < 30% in all arms)
Silverstone 2001[36]	156	Moclobemide 450–750 mg/d Imipramine 150–250 mg/d	8 weeks	HAM-D change from baseline	Moclobemide: 9.9 Imipramine: 13.0	Moclobemide: 3.7% Imipramine: 11%	No placebo control
Thase et al 1992[139]	16	Tranylcypromine >30 mg/d Imipramine >150 mg/d Crossover study from imipramine to tranylcypromine and vice versa in those non-responding in the initial study [29]	6-week cross-over study following [35]	Beck Depression Inventory; HAM-D score, Reversed vegetative symptom scale	75% "responder" for switch IMI-TCP, 25% "responder" for switch TCP-IMI	Treatment emergent mania: 1/4 patients switched to IMI (25%)	No Placebo control, primary outcome and response criterion unclear, highly selected population (IMI or TCP non responder with anergic bipolar depression)
Tohen et al. 2003[102]	833, 86 with OFC	Fluoxetine 20–50 mg/d together with olanzapine (6 or 12 mg/7d)	8 weeks	Changes in MADRS total scores (MMRM analysis)	Placebo: -11.9 Olanzapine:-15.0 OFC:-18.5 OFC was significantly superior both to Placebo and	Placebo: 6.7% Olanzapine: 5.7% OFC: 6.4% No significant differences	Probably best positive evidence from a RCT for the efficacy of an antidepressant in bipolar depression. CAVE: Not a monotherapy study, augmenting effects of olanzapine are possible.
Vieta et al 2002[41]	60	Paroxetine: 20–60 mg/d Venlafaxine: 75–450 mg/d	6 weeks	Response: ≥50% decrease from baseline to endpoint HAM-D score	Paroxetine: 43% responders Venlafaxine: 48%	Paroxetine: 3% Venlafaxine: 13%	No placebo control
Yatham et al 2016 [46]	344 (172 on agomelatine)	Agomelatine 25-50mg/d Placebo Both add on to lithium or valproate	8 weeks	Changes in MADRS total scores (ITT-analysis)	Agomelatine: -15.4 Placebo: -15.2 No significant difference	Agomelatine 4.1% Placebo 3.5%	Unclear whether a truly negative or failed study (strong centre effects leading to a placebo-response rate of 61%)

treatment [57] and may deserve greater attention from clinicians. The most robust indicator of risk for TEAS, however, is the presence of even very subtle manic symptoms while depressed [58]. In the STEP-BD study, for each 1-point increase in baseline Young mania rating scale (YMRS) score, the hazard for TEAS increased by ~6% [57].

Similar to TEAS, the issue of potential cycle acceleration by antidepressants has not been solved so far in an unambiguous way. Following

early reports of massive cycle acceleration with TCA [59], later studies could not always replicate this finding and do rather point towards relapse preventive effects of antidepressants in certain patient populations [31,60,61].

The issue of increased suicidality and, probably, suicide with antidepressants has been extensively debated for unipolar depression, and current consensus is that, apart from adolescents, antidepressants are rather protective against suicide than promoting it [62,63]. Little research into this issue has been done so far for bipolar depression; however, data from the STEP-BD study do not support an increase in suicidality in bipolar patients initiated on antidepressants [64].

Maintenance treatment and prevention of recurrence of bipolar depression are beyond the scope of this article on acute treatment; however, as a rule of thumb, acute treatment should ideally be initiated with a drug that has also proven maintenance efficacy. Unfortunately, maintenance and prophylaxis of bipolar depression are even less rigorously studied than acute treatment. The use of antidepressants as primary and sole maintenance treatment has been discouraged as its efficacy and potential of inducing TEAS are controversial [31]. Across trials, a major hurdle of assessing the risk of TEAS with long term antidepressant treatment is the lack of a uniform definition of time window and threshold severity of manic symptoms to be counted as TEAS [65]. In the absence of good quality evidence, experts agree that combination of a mood stabilizer with the long-term use of antidepressants may be appropriate in patients relapsing after antidepressant discontinuation, especially if discontinuation had been gradual [31].

Mood Stabilizers

■ Lithium

Earlier studies in bipolar depression indicated that lithium has antidepressant effects superior to placebo and is more effective in bipolar than unipolar depression [66], but based on more recent studies, it's clinical effectiveness as monotherapy in acute bipolar depression is modest [67,68]. A further concern is that abrupt lithium discontinuation after successful treatment may induce early relapse [69]. Nevertheless, given the limited choice of treatments, lithium is still recommended as a first-line therapy for acute bipolar depression in some guidelines [32,70];

Historic data suggest that lithium has a lesser efficacy in treating the depressive than the manic phase in bipolar disorder [71-73] which is also resembled by its potential inferior prophylactic efficacy against bipolar depression compared to mania [74,75].

Lithium's potential lack of acute antidepressant efficacy was more recently also demonstrated by the EMBOLDEN I study [68] where lithium's effect wasn't superior to placebo in reducing the MADRS total score (NNT for response to lithium=15). One factor limiting the validity of this finding is the low median serum concentration of lithium in this study (0.61 mmol/l). Only 64 % of all patients attained potentially sufficient serum lithium concentration (≥0.6 mmol/l) [19]. A take home message from the study by Nemeroff et al [76], however, was that only high lithium levels >0.8 mmol/l may have sufficient antidepressant effects that override any additional benefits from imipramine or paroxetine.

In summary, efficacy data for acute lithium monotherapy are contradictory right now. Lithium augmentation of ongoing antidepressant treatment has not been researched in bipolar depression to a similar degree as it has in unipolar depression [77]; as a matter of fact, there is no published placebo-controlled lithium augmentation study including bipolar depressed patients only. This is of special note as naturalistic data suggest that so far undiscovered bipolarity is related to a positive response to lithium augmentation in treatment-resistant major depression [78]. However, there is still an important role for lithium in bipolar depression, as it is known to be protective against suicide [79]. But to maximize this effect, higher levels between 0.8-1.2 mmol/l are recommended. Such levels, however, are often poorly tolerated by patients and may carry an increased risk of neurotoxicity.

■ Lamotrigine

Lamotrigine was first endorsed as a first line acute treatment for bipolar depression by the American Psychiatric Association (APA) in 2002 [80], and continues to be considered as such in some recent guideline [3,32,70] whereas others have dismissed it [17,81].

All five trials of lamotrigine in acute bipolar depression were negative (three in Bipolar I, one in Bipolar II and one in a mixed population of Bipolar I and II patients) concerning the

primary outcomes but some showed benefit on the basis of secondary outcomes (on the basis of these secondary outcomes, response rates in one trial were 50 % for lamotrigine and double of those for placebo) [82]. Pooled data from all five studies also suggest a modest, but probably not clinically significant acute antidepressant effect of lamotrigine [83]. The apparently delayed antidepressant response to lamotrigine might be due to the slow titration scheme to avoid allergic reactions, ranging from skin rash to Steven-Johnson syndrome. Thus, longer observation periods than the traditional 6-8 weeks in acute depression trials and selecting more severely depressed patients at trial entry may favor differentiation of response to lamotrigine from placebo.

How does lamotrigine compare to other, either licensed or at least recommended treatments of bipolar depression?

There are no comparative studies of lamotrigine against quetiapine or lurasidone. A seven-week, double-blind RCT of a fixed dose olanzapine-fluoxetine combination (OFC, n = 205) and lamotrigine (n= 205) in acutely depressed Bipolar I patients was conducted to determine efficacy and tolerability in direct comparison. Patients receiving OFC had significantly greater improvement than lamotrigine-treated patients on the Clinical Global Impressions-Severity of Illness scale (primary outcome), MADRS and YMRS total scores, the latter suggestive of better efficacy in mixed depressive patients and/or lower rates of TEAS with OFC. However, side effects (somnolence, increased appetite, dry mouth, sedation, weight gain, and tremor) occurred significantly more frequently with OFC than lamotrigine, and weight, total cholesterol, and triglyceride levels were also significantly elevated in OFC-treated patients compared with lamotrigine-treated patients. So, in summary, OFC was more effective, but lamotrigine was better tolerated [84].

A single-blind study by Suppes et al. 2008 [85] compared lamotrigine to lithium in Bipolar II patients. Both treatment arms improved in terms of depressive symptomatology. While lithium treatment was associated with higher rates of adverse effects, there were no significant differences in efficacy between the two groups.

■ Sodium Valproate & Carbamazepine

Data regarding these two medications is limited. There are some studies supporting the superiority of sodium valproate over placebo in treating acute bipolar depression [86]; despite the fact that the antidepressant effect is moderate at its best, sodium valproate has been endorsed by recent guidelines [87]. Sodium valproate also has low to moderate efficacy in protecting against future depressive episodes [88-90].

A recent meta-analysis found that efficacy data for the acute treatment of bipolar depression were encouraging for both sodium valproate and carbamazepine [25]. However, in general the quality of acute bipolar depression treatment studies with carbamazepine is poor, there is only one randomized comparison study against placebo [91]. In addition, there are no established data concerning its dosage and plasma levels for the treatment of acute depression [72]. For relapse and recurrence prevention carbamazepine appears to be less effective than lithium [92-97].

Antipsychotics

The newer second generation (atypical) antipsychotics (SGAs) are considered to have a more favorable adverse effects profile compared to typical antipsychotics [98]. Several studies support their usefulness during all phases of bipolar illness, both as monotherapy and as an adjunct to mood stabilizers [72-99]. The mechanism of antidepressant action of some SGAs is not fully understood and may vary between drugs; some of the SGA may exert their antidepressant effect by affecting the serotonergic neurotransmission, such as olanzapine and quetiapine [100].

Both olanzapine as monotherapy and a fixed dose combination of olanzapine and fluoxetine (OFC) are now treatments approved in several countries for bipolar depression, based on positive RCTs [101-105].

The bulk of evidence in the acute treatment of bipolar depression, however, rests with quetiapine. Quetiapine was the first medication with a specific label for acute treatment of bipolar depression based on six double-blind, randomized placebo controlled studies, out of which five were successful and only one study in adolescents [106] failed. Quetiapine has first proven antidepressant efficacy in two 8-week placebo-controlled studies, the so called 'Bolder' studies [107,108]. These initial results were then confirmed in two additional, placebo- and active comparator controlled studies, the "Embolden" studies [50,68], as well as another

placebo-controlled study using extended release quetiapine [109]. Of note, Quetiapine has also been approved by the US FDA for the treatment of acute bipolar II depression based on posthoc subanalyses of the pivotal RCTs. However, both for olanzapine and quetiapine somnolence and weight gain can be important contributing factor for discontinuation of those medications. These side effects are not associated with lurasidone, which recently gained FDA approval for the acute treatment of Bipolar I depression as monotherapy or as add-on to lithium or valproate. This labelling was based on two positive large scale, placebo-controlled studies [110,111]. The effect size of 0.51 in monotherapy is moderate and smaller than that of quetiapine or OFC, but the tolerability and safety profile appear better than with the other approved treatments. However, akathisia was more frequently observed in these studies with lurasidone than with placebo and might impact on treatment adherence [112]. Nevertheless, when balancing potential benefits against harm, lurasidone comes out as a more favourable treatment for bipolar depression than quetiapine, Olanzapine-Fluoxetine combination or lamotrigine [113]. Most recently, a Phase IIB study (ClinicalTrials.gov Identifier: NCT01396447) demonstrated significant antidepressant effects for cariprazine (1.5mg/d) in Bipolar I depression [114]. Results of further Phase III studies still have to be awaited. Both lurasidone and cariprazine are mentioned only in very recent guidelines [3,115] as the number of studies continues to be low, and licence and marketing status still differ between countries.

Other antipsychotics like aripiprazole could show only transient effects up to week 6 by reducing the depressive symptoms significantly as opposed to placebo [116], however, no difference was noted at week 8 (endpoint of the trial). Akathisia may also become problematic with Aripiprazole [117].

Similar to aripiprazole, also ziprasidone failed in a pivotal study in acute bipolar depression to separate from placebo [118].

More recently, and with the emergence of the DSM5 "Specifier"category, bipolar depression with a mixed manic features gained the attention it deserves. Mixed bipolar depression is common [119], but little is known about its adequate treatment. Antidepressants may worsen manic features especially in these patients [52], and little is known about the efficacy of classical mood stabilizers such as lithium, valproate or lamotrigine. A recent meta-analysis including seven studies suggests that atypical antipsychotics may constitute the currently best available treatment [10] but more research is clearly needed.

Experimental treatment options

Wakefulness-Promoting Agent like modafinil or the longer lasting isomer armodafinil have an adjunctive role in treating bipolar depression. Modafinil add-on [120] was found effective in improving depressive symptoms in bipolar patients who didn't respond to a mood stabilizer, with or without concomitant antidepressants. In this study, the risk to cause mania was not different to placebo. Two further studies with adjunctive armodafinil gave preliminary evidence of its efficacy as adjunct to mood stabilizers. The first study, although positive, is difficult to interpret due to a statistically significant treatment-by-baseline interaction as found by using analysis of variance (ANOVA) [121]. A second study in treatment refractory bipolar depression, however, confirmed a significant difference on the Inventory of depressive symptoms-clinician version (IDS-C) between armodafinil and placebo, starting at week 7 [122]. The NNT was 9, but given the treatment refractory sample, this can still be considered as clinically relevant. Unfortunately, a final large proof of concept study with amodafinil add-on to ongoing maintenance treatment in acute break through depression failed to show a significant advantage against placebo [123]; thus, the current evidence is inconclusive.

Pramipexole, a dopamine 2/3 receptor agonist, was found effective compared to placebo in Bipolar II depression [124] and in a small sample of patients with treatment refractory bipolar depression [125], however, reports of intolerability and mood switch into hypomania/mania are not uncommon [126].

More recent, memantine has been tested as an adjunctive treatment in bipolar depression. Experimental evidence suggests that memantine may lower elevated TNF-Alpha serum levels in bipolar II patients, and thus may exert not only anti-inflammatory, but also mood stabilising effects [127]. However, metaanalysis of two RCTs with memantine add-on in bipolar depression showed no significant advantage over placebo [128].

Omega-3 fatty acids were found to have an effect

on reducing depressive symptoms in both bipolar and unipolar depression [129]. The outcomes of single studies, however, were contradictory, and dosing of ethyl-eicosapentanoate may play an important role [130]. As part of a healthy diet they may need to be consumed in higher doses, due to their small effect size [131].

Subthreshold hypothyroidsm might play a role in treatment refractory bipolar depression. Both lower values of free thyroxin index and higher values of TSH were significantly associated with longer time to remission during treatment with mood stabilizer [132]. Consequently, supraphysiological doses of thyroxine (T3) or levothyroxine (T4) have been studied as augmentative treatment in depression. The only placebo controlled study in bipolar depression, however, pointed to benefits of such a treatment in female patients only [133].

Non-pharmacalogical treatments of bipolar depression include psychotherapies and physical treatments such as light therapy, sleep phase advance treatment, ECT and others. They can be highly effective, as ECT, but are usually reserved for a small minority of patients with treatment refractory bipolar depression. For this reason, they are not included in this article, but further information on their indication, efficacy and tolerability can be found in recent reviews [17,19].

Conclusion and Future Perspective

Depressive symptoms in bipolar disorder are usually undistinguishable from symptoms of unipolar depression; therefore, in the absence of a clear history of mania or hypomania, a probabilistic approach towards the diagnosis might be required.

Informed treatment decision should be based on strong evidence; however, for the acute treatment of bipolar depression, evidence is still scarce, especially for older treatment options, and only recently more rigorous studies have been conducted with newer agents. Furthermore, the relative lack of head-to-head comparisons also limits and clear guidance for individual treatment plans. As mentioned, there is some ambiguity about the role of certain medications, especially antidepressants. Adopting evidence based strategy in the treatment can generate a positive outcome, or at least avoid undesirable complications. For example, monotherapy antidepressants are not recommended for varying reasons, ranging from doubts about efficacy to worries about TEAS.

But we have to acknowledge that there are certain limitations, which influenced this general impression about antidepressants, such as the design of the studies and doses used. This controversy extends to other groups of medications. Lithium, for example, may be not first choice in treating acute bipolar depression, however, lithium's role in protecting against suicide is very important. Lamotrigine as acute treatment has a modest role, too, and it is less effective than combinations such as olanzapine /fluoxetine (OFC), although it is better tolerated compared to OFC as well as to lithium. Lamotrigine's other limitation is the requirement for a slow titration. Whereas there are some encouraging data to support the use of sodium valproate, some controversy exists about the value of carbamazepine.

Some SGA alone or combined with antidepressant appear to exert a significant benefit in the treatment of bipolar depression. Olanzapine, olanzapine/ fluoxetine combination and quetiapine have proven to be effective, but tolerability can be an issue. Lurasidone appear to be promising, especially as it is well tolerated with fewer metabolic side effects; however, lurasidone's effect size is smaller than the one of quetiapine, and akathisia might have an impact on the adherence. Cariprazine may become an additional future choice. Other treatments like Wakefulness-Promoting Agents, Dopamine 2/3 receptor agonist, Common Omega-3 fatty acids and supraphysiological levels of thyroxine can augment the treatment of bipolar depression. We also need to keep nonpharmacological, physical treatments as an effective option in mind as well as adjunctive psychotherapy. Involving the patient and his family in all treatment planning is crucial to ensure cooperation and adherence.

Abbreviations

ANOVA: Analysis of variance

APA: American Psychiatric Association

CI: Confidence interval

DSM: Diagnostic and Statistical Manual of Mental Disorders

ECT: Electroconvulsive treatment

FDA: Food & Drug Administration

HDRS: Hamilton Depression Rating Scale

ICD: International Classification of Diseases

IDS-C: Inventory of depressive symptoms-clinician version

IMI: Imipramine

MADRS: Montgomery-Åsberg Depression Rating Scale

MDE: Major depressive episode

NNT: Number needed to treat

OFC: Olanzapine Fluoxetine Combination

PAR: Paroxetine

RCT: Randomised controlled trial

RR: Responder rate

rTMS: Repetitive transcranial magnetic stimulation

SGAs: Second generation (atypical) antipsychotics

SNRI's: Serotonin–norepinephrine re-uptake inhibitors

SSRIs: Selective serotonin reuptake inhibitors

STEP-BD: Systematic Treatment Enhancement Program for Bipolar Disorder

TCA: Tricyclic antidepressants

TEAS: Treatment Emergent Affective Switch

TSH: Thyroid stimulating hormone

WFSBP: World federation of societies of biological psychiatry

YMRS: Young mania rating scale

Competing interests

Dr. Zeid Mohammed declares that he has no competing interests

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References

1. Bas TO, Poyraz CA, Bas A, *et al.* The impact of cognitive impairment, neurological soft signs and subdepressive symptoms on functional outcome in bipolar disorder. *J. Affect. Disord* 174(1), 336-41 (2015).
2. Judd LL, Akiskal HS, Schettler PJ, *et al.* Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch. Gen. Psychiatry* 62(12), 1322-1330 (2005).
3. Goodwin GM, Haddad PM, Ferrier IN, *et al.* Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *J. Psychopharmacol* 30(6), 495-553 (2016).
4. Kupfer DJ, Frank E, Grochocinski VJ, *et al.* Stabilization in the treatment of mania, depression and mixed states. *Acta. Neuropsychiatrica* 12(1), 3-114 (2000).
5. Solomon DA, Leon AC, Coryell WH, *et al.* Longitudinal course of bipolar I disorder: duration of mood episodes. *Arch. Gen. Psychiatry* 67(1), 339-347 (2010).
6. Vazquez GH, Holtzman JN, Tondo L, *et al.* Efficacy and tolerability of treatments for bipolar depression. *J. Affect. Disord* 183(1), 258-62 (2015).
7. National Collaborating Centre for Mental Health. Bipolar disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. CG185: NICE Guideline. National Institute for Health and Clinical Excellence, London 2014.
8. Tondo L, Vazquez GH, Baldessarini RJ. Options for pharmacological treatment of refractory bipolar depression. *Curr. Psychiatry. Rep* 16(2), 431 (2014).
9. Taylor DM, Cornelius V, Smith L, *et al.* Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta. Psychiatr. Scand* 130(1), 452-469 (2014).
10. Fornaro M, Stubbs B, De BD, *et al.* Atypical Antipsychotics in the Treatment of Acute Bipolar Depression with Mixed Features: A Systematic Review and Exploratory Meta-Analysis of Placebo-Controlled Clinical Trials. *Int. J. Mol. Sci* 17(2), 241 (2016).
11. Zimmerman M, Ruggero CJ, Chelminski I, *et al.* Is bipolar disorder overdiagnosed? *J. Clin. Psychiatry* 69(1), 935-940 (2008).
12. Hantouche EG, Akiskal HS, Lancrenon S, *et al.* Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study (EPIDEP). *J. Affect. Disord* 50(2-3), 163-173 (1998).
13. First MB, Gibbon M. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II. In: Hilsenroth,M. and Segal,D. (eds.), Comprehensive handbook of psychological assessment, Personality assessment. John Wiley & Sons, Inc., Hoboken, NJ 2, 134-143 (2004).
14. Hirschfeld RM, Williams JB, Spitzer RL, *et al.* (2000) Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am. J. Psychiatry* 157(11), 1873-1875.
15. Angst J, Adolfsson R, Benazzi F, *et al.* The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. *J. Affect. Disord* 88(2), 217-233 (2005).

16. Winokur G, Coryell W, Endicott J, *et al.* Further distinctions between manic-depressive illness (bipolar disorder) and primary depressive disorder (unipolar depression). *Am. J. Psychiatry* 150(8), 1176-1181 (1993).
17. Grunze H, Vieta E, Goodwin GM, *et al.* The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* 11(2), 81-109 (2010).
18. Perlis RH, Brown E, Baker RW, *et al.* Clinical features of bipolar depression versus major depressive disorder in large multicenter trials. *Am. J. Psychiatry* 163(2), 225-231 (2006).
19. Bauer M, Ritter P, Grunze H, *et al.* Treatment options for acute depression in bipolar disorder. *Bipolar. Disord* 14 (Suppl 2), 37-50 (2012).
20. Mitchell PB, Goodwin GM, Johnson GF, *et al.* Diagnostic guidelines for bipolar depression: a probabilistic approach. *Bipolar. Disord* 10(1 Pt 2), 144-152 (2008).
21. Yatham LN, Kennedy SH, Schaffer A, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar. Disord* 11(3), 225-255 (2009).
22. Angst F, Stassen HH, Clayton PJ, *et al.* Mortality of patients with mood disorders: follow-up over 34-38 years. *J. Affect. Disord* 68(2-3), 167-181 (2002).
23. Plante DT and Winkelman JW. Sleep disturbance in bipolar disorder: therapeutic implications. *Am. J. Psychiatry* 165(7), 830-843 (2008).
24. Grunze H. Treatment of acute bipolar depression: A European viewpoint. *J. Bipolar. Disorder* 5(1), 17 (2007).
25. Selle V, Schalkwijk S, Vazquez GH, *et al.* Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. *Pharmacopsychiatry* 47(2), 43-52 (2014).
26. Sassi RB and Soares JC. Emerging therapeutic targets in bipolar mood disorder. *Expert. Opin. Ther. Targets* 5(5), 587-599 (2001).
27. Judd LL and Akiskal HS. Depressive episodes and symptoms dominate the longitudinal course of bipolar disorder. *Curr. Psychiatry. Rep* 5(6), 417-418 (2003).
28. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am. J. Psychiatry* 161(9), 1537-1547 (2004).
29. Sidor MM and MacQueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J. Clin. Psychiatry* 72(2), 156-167 (2011).
30. Vazquez GH, Tondo L, Undurraga J, *et al.* Overview of antidepressant treatment of bipolar depression. *Int. J. Neuropsychopharmacol* 16(7), 1673-1685 (2013).
31. 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* 170(11), 1249-1262 (2013).
32. Yatham LN, Kennedy SH, Parikh SV, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar. Disord* 15(1), 1-44 (2013).
33. Ghaemi SN, Wingo AP, Filkowski MA, *et al.* Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. *Acta. Psychiatr. Scand* 118(5), 347-356 (2008).
34. Grunze H. Reevaluating therapies for bipolar depression. *J. Clin. Psychiatry* 66(Suppl 5), 17-25 (2005).
35. Himmelhoch JM, Thase ME, Mallinger AG, *et al.* Tranylcypromine versus imipramine in anergic bipolar depression. *Am. J. Psychiatry* 148(7), 910-916 (1991).
36. Silverstone T. Moclobemide vs. imipramine in bipolar depression: a multicentre double-blind clinical trial. *Acta. Psychiatr. Scand* 104(2), 104-109 (2001).
37. Sachs GS, Lafer B, Stoll AL, *et al.* A double-blind trial of bupropion versus desipramine for bipolar depression. *J. Clin. Psychiatry* 55(9), 391-393 (1994).
38. Amsterdam J. Efficacy and safety of venlafaxine in the treatment of bipolar II major depressive episode. *J Clin Psychopharmacol* 18(5), 414-417 (1998).
39. Amsterdam JD and Garcia-Espana F. Venlafaxine monotherapy in women with bipolar II and unipolar major depression. *J. Affect. Disord* 59(3), 225-229 (2000).
40. Amsterdam JD and Brunswick DJ. Antidepressant monotherapy for bipolar type II major depression. Bipolar Disord 5(6), 388-395 (2003).
41. Vieta E, Martinez-Aran A, Goikolea JM, *et al.* A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. *J. Clin. Psychiatry* 63(6), 508-512 (2002).
42. Post RM, Altshuler LL, Leverich GS, *et al.* Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br. J. Psychiatry* 189(1), 124-131 (2006).
43. Chen J, Fang Y, Kemp DE, *et al.* Switching to hypomania and mania: differential neurochemical, neuropsychological, and pharmacologic triggers and their mechanisms. *Curr. Psychiatry. Rep* 12(6), 512-521 (2010).
44. Calabrese JR, Guelfi JD, Perdrizet-Chevallier C. Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. *Bipolar. Disord* 9(6), 628-635 (2007).
45. Fornaro M, McCarthy MJ, De BD, *et al.* Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: a preliminary open label study. *Neuropsychiatr. Dis. Treat* 9(!), 243-51 (2013).
46. Yatham LN, Vieta E, Goodwin GM, *et al.* Agomelatine or placebo as adjunctive therapy to a mood stabiliser in bipolar I depression: randomised double-blind placebo-controlled trial. *Br. J. Psychiatry* 208(1), 78-86 (2016).
47. Bottlender R, Rudolf D, Jager M, *et al.* Are bipolar I depressive patients less responsive to treatment with antidepressants than unipolar depressive patients? Results from a case control study. *Eur. Psychiatry* 17(4), 200-205 (2002).
48. Tondo L, Baldessarini RJ, Vazquez G, *et al.* Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. *Acta. Psychiatr. Scand* 127(5), 355-364 (2013).
49. Farrelly N, Sachs G, Möller HJ, *et al.* Recent advances in the treatment of bipolar depression. *Clin Approaches Bipolar Disord* 6(1), 20-27 (2007).
50. McElroy SL, Weisler RH, Chang W, *et al.* A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J. Clin. Psychiatry* 71(2), 163-174 (2010).
51. Sachs GS, Nierenberg AA, Calabrese JR, *et al.* Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N. Engl. J. Med* 356(1), 1711-1722 (2007).
52. El-Mallakh RS, Ghaemi SN, Sagduyu K, *et al.* Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. *J. Affect. Disord* 111(2-3), 372-377 (2008).
53. Truman CJ, Goldberg JF, Ghaemi SN, *et al.* Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *J. Clin. Psychiatry* 68(10), 1472-1479 (2007).
54. Bottlender R, Rudolf D, Strauß A, *et al.* Antidepressant-associated maniform states in acute treatment of patients with bipolar I depression. *Eur. Arch. Psychiatry. Clin. Neurosci* 248(6), 296-300 (1998).
55. Bond DJ, Noronha MM, Kauer-Sant'Anna M, *et al.* Antidepressant-Associated Mood Elevations in Bipolar II Disorder Compared With Bipolar I Disorder and Major Depressive Disorder: A Systematic Review and Meta-Analysis. *J. Clin. Psychiatry* 69(10), 1589-1601 (2008).
56. 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* 18(3), 243-249 (2012).

57. Perlis RH, Ostacher MJ, Goldberg JF, Miklowitz DJ et al. (2010) Transition to mania during treatment of bipolar depression. Neuropsychopharmacology 35: 2545-2552.

58. Frye MA, Helleman G, McElroy SL, *et al.* Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am. J. Psychiatry* 166(2), 164-172 (2009).

59. Wehr TA and Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch. Gen. Psychiatry* 36(5), 555-559 (1979).

60. Coryell W, Solomon D, Turvey C, *et al.* The long-term course of rapid-cycling bipolar disorder. *Arch. Gen. Psychiatry* 60(9), 914-920 (2003).

61. Altshuler LL, Post RM, Hellemann G, *et al.* Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: a blinded, randomized study. *J. Clin. Psychiatry* 70(4), 450-457 (2009).

62. Sartorius N, Baghai TC, Baldwin DS, *et al.* Antidepressant medications and other treatments of depressive disorders: a CINP Task Force report based on a review of evidence. *Int. J. Neuropsychopharmacol* 10(1), 01-207 (2007).

63. Möller HJ, Baldwin DS, Goodwin G, *et al.* Do SSRIs or antidepressants in general increase suicidality? WPA Section on Pharmacopsychiatry: consensus statement. *Eur. Arch. Psychiatry. Clin. Neurosci* 258(3), 03-23 (2008).

64. Bauer MS, Wisniewski SR, Marangell LB, *et al.* Are Antidepressants Associated With New-Onset Suicidality in Bipolar Disorder? A Prospective Study of Participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *J. Clin. Psychiatry* 67(1), 48-55 (2006).

65. Tohen M, Frank E, Bowden CL, *et al.* The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar. Disord* 11(5), 453-473 (2009).

66. Zornberg GL and Pope HG. Treatment of depression in bipolar disorder: new directions for research. *J. Clin. Psychopharmacol* 13(6), 397-408 (1993).

67. Grunze H. Lithium in the acute treatment of bipolar disorders-a stocktaking. *Eur. Arch. Psychiatry. Clin. Neurosci* 253(3), 115-119 (2003).

68. Young AH, McElroy SL, Bauer M, *et al.* A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J. Clin. Psychiatry* 71(2), 150-162 (2010).

69. Suppes T, Baldessarini RJ, Faedda GL, *et al.* Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Arch. Gen. Psychiatry* 48(12), 1082-1088 (1991).

70. Malhi GS, Bassett D, Boyce P, *et al.* Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust. N Z. J. Psychiatry* 49(12), 1087-1206 (2015).

71. Calabrese JR, Vieta E, Shelton MD. Latest maintenance data on lamotrigine in bipolar disorder. *Eur. Neuropsychopharmacol* 13(2), 57-66 (2003).

72. Fountoulakis KN, Grunze H, Panagiotidis P, *et al.* Treatment of bipolar depression: an update. *J. Affect. Disord* 109(1), 21-34 (2008).

73. Bauer MS, Callahan AM, Jampala C, *et al.* Clinical practice guidelines for bipolar disorder from the Department of Veterans Affairs. *J. Clin. Psychiatry* 60(1), 9-21 (1999).

74. Vieta E, Gunther O, Locklear J, *et al.* Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. *Int. J. Neuropsychopharmacol* 14(8), 1029-1049 (2011).

75. Goodwin GM, Bowden CL, Calabrese JR, *et al.* A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J. Clin. Psychiatry* 65(3), 432-441 (2004).

76. Nemeroff CB, Evans DL, Gyulai L, *et al.* Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am. J. Psychiatry* 158(6), 906-912 (2001).

77. Crossley NA and Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J. Clin. Psychiatry* 68(6), 935-940 (2007).

78. Inoue T, Abekawa T, Nakagawa S, *et al.* Long-term naturalistic follow-up of lithium augmentation: relevance to bipolarity. *J. Affect. Disord* 129(1-3), 64-67 (2011).

79. Cipriani A, Hawton K, Stockton S, *et al.* Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 346(1), f3646 (2013).

80. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am. J. Psychiatry* 159(4), 1-50 (2002).

81. Fountoulakis KN, Kasper S, Andreassen O, *et al.* Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry. *Eur. Arch. Psychiatry. Clin. Neurosci* 262(1), 1-48 (2012).

82. Calabrese JR, Huffman RF, White RL, *et al.* Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar. Disord* 10(2), 323-333 (2008).

83. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br. J. Psychiatry* 194(1), 4-9 (2009).

84. Brown EB, McElroy SL, Keck PE, *et al.* A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J. Clin. Psychiatry* 67(7), 1025-1033 (2006).

85. Suppes T, Marangell LB, Bernstein IH, *et al.* A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. *J. Affect. Disord* 111(2-3), 334-343 (2008).

86. Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. *J. Affect. Disord* 124(3), 228-234 (2010).

87. Kohler S, Gaus S, Bschor T. The challenge of treatment in bipolar depression: evidence from clinical guidelines, treatment recommendations and complex treatment situations. *Pharmacopsychiatry* 47(2), 53-59 (2014).

88. Gyulai L, Bowden CL, McElroy SL, *et al.* Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology* 28(7), 1374-1382 (2003).

89. Puzynski S and Klosiewicz L. Valproic acid amide as a prophylactic agent in affective and schizoaffective disorders. *Psychopharmacol. Bull* 20(1), 151-159 (1984).

90. Solomon DA, Ryan CE, Keitner GI, *et al.* A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. *J. Clin. Psychiatry* 58(3), 95-99 (1997).

91. Zhang ZJ, Kang WH, Tan QR, *et al.* Adjunctive herbal medicine with carbamazepine for bipolar disorders: A double-blind, randomized, placebo-controlled study. *J. Psychiatr. Res* 41(3-4), 360-369 (2007).

92. Coxhead N, Silverstone T, Cookson J. Carbamazepine versus lithium in the prophylaxis of bipolar affective disorder. *Acta. Psychiatr. Scand* 85(2), 114-118 (1992).

93. Denicoff KD, Smith-Jackson EE, Disney ER, *et al.* Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J. Clin. Psychiatry* 58(11), 470-478 (1997).

94. Greil W, Ludwig-Mayerhofer W, Erazo N, *et al.* Lithium versus carbamazepine in the maintenance treatment of bipolar disorders-a randomised study. *J. Affect. Disord* 43(2), 151-161 (1997).

95. Greil W, Kleindienst N, Erazo N, *et al.* Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. *J. Clin. Psychopharmacol* 18(6), 455-460 (1998).

96. Hartong EG, Moleman P, Hoogduin CA, *et al.* Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. *J. Clin. Psychiatry* 64(2), 144-151 (2003).

97. Watkins SE, Callender K, Thomas DR, *et al.* The effect of carbamazepine and lithium on remission from affective illness. *Br. J. Psychiatry* 150(1), 180-182 (1987).

98. Seemüller F, Forsthoff A, Dittmann S, *et al.* The safety and tolerability of atypical antipsychotics in bipolar disorder. *Expert. Opin. Drug. Saf* 4(1), 849-868 (2005).

99. Tohen M and Vieta E. Antipsychotic agents in the treatment of bipolar mania. *Bipolar. Disord* 11(2), 45-54 (2009).

100. Yatham LN, Goldstein JM, Vieta E, *et al.* Atypical antipsychotics in bipolar depression: potential mechanisms of action. *J. Clin. Psychiatry* 66(5), 40-48 (2005).

101. Tohen M, Katagiri H, Fujikoshi S, *et al.* Efficacy of olanzapine monotherapy in acute bipolar depression: a pooled analysis of controlled studies. *J. Affect. Disord* 149(1-3), 196-201 (2013).

102. Tohen M, Vieta E, Calabrese J, *et al.* Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch. Gen. Psychiatry* 60(11), 1079-1088 (2003).

103. Tohen M, McDonnell DP, Case M, *et al.* Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. *Br. J. Psychiatry* 201(5), 376-382 (2012).

104. Detke HC, DelBello MP, Landry J, *et al.* Olanzapine/Fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J. Am. Acad. Child. Adolesc. Psychiatry* 54(3), 217-224 (2015).

105. Wang M, Tong JH, Huang DS, *et al.* Efficacy of olanzapine monotherapy for treatment of bipolar I depression: a randomized, double-blind, placebo controlled study. *Psychopharmacology. (Berl)* 231(14), 2811-2818 (2014).

106. DelBello MP, Chang K, Welge JA, *et al.* A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar. Disord* 11(5), 483-493 (2009).

107. Thase ME, Macfadden W, Weisler RH, *et al.* Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J. Clin. Psychopharmacol* 26(6), 600-609 (2006).

108. Calabrese JR, Keck PE Jr, Macfadden W, *et al.* A Randomized, Double-Blind, Placebo-Controlled Trial of Quetiapine in the Treatment of Bipolar I or II Depression. *Am. J. Psychiatry* 162(7), 1351-1360 (2005).

109. Suppes T, Datto C, Minkwitz M, *et al.* Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *J. Affect. Disord* 121(1-2), 106-115 (2010).

110. Loebel A, Cucchiaro J, Silva R, *et al.* Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am. J. Psychiatry* 171(2), 169-177 (2014).

111. Loebel A, Cucchiaro J, Silva R, *et al.* Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am. J. Psychiatry* 171(2), 160-168 (2014).

112. 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* 155(1), 20-27 (2014).

113. Ketter TA, Miller S, Dell'Osso B, *et al.* Balancing benefits and harms of treatments for acute bipolar depression. *J. Affect. Disord* 169(1), S24-33 (2014).

114. Durgam S, Earley W, Lipschitz A, *et al.* An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients with Bipolar I Depression. *Am. J. Psychiatry* 173(3), 271-281 (2016).

115. Fountoulakis K, Yatham L, Grunze H, *et al.* The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017), Part 2: Review, grading of the evidence and a precise algorithm. *Int. J. Neuropsychopharmacol* (2016).

116. Thase ME, Jonas A, Khan A, *et al.* Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J. Clin. Psychopharmacol* 28(1), 13-20 (2008).

117. Gao K, Kemp DE, Fein E, *et al.* Number needed to treat to harm for discontinuation due to adverse events in the treatment of bipolar depression, major depressive disorder, and generalized anxiety disorder with atypical antipsychotics. *J. Clin. Psychiatry* 72(8), 1063-1071 (2011).

118. Sachs GS, Ice KS, Chappell PB, *et al.* Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J. Clin. Psychiatry* 72(10), 1413-1422 (2011).

119. Goldberg JF, Perlis RH, Bowden CL, *et al.* Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am. J. Psychiatry* 166(2), 173-181 (2009).

120. Frye MA, Grunze H, Suppes T, *et al.* A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am. J. Psychiatry* 164(8), 1242-1249 (2007).

121. Calabrese JR, Ketter TA, Youakim JM, *et al.* Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. *J. Clin. Psychiatry* 71(10), 1363-1370 (2010).

122. Calabrese JR, Frye M, Yang R, *et al.* A Double-Blind, Placebo-Controlled, Multicenter Trial of Adjunctive Armodafinil in Adults With Major Depression Associated With Bipolar I Disorder. The American College of Neuropsychopharmacology 51st Annual Meeting, Hollywood, FL , USA (2012).

123. Ketter TA, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder. *J. Affect. Disord* 181(1), 87-91 (2015).

124. Zarate CA Jr, Payne JL, Singh J, *et al.* Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol. Psychiatry* 56(1), 54-60 (2004).

125. 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* 161(3), 564-566 (2004).

126. Dell'Osso B and Ketter TA. Assessing efficacy/effectiveness and safety/tolerability profiles of adjunctive pramipexole in bipolar depression: acute versus long-term data. *Int. Clin. Psychopharmacol* 28(6), 297-304 (2013).

127. Lee SY, Chen SL, Chang YH, *et al.* The effects of add-on low-dose memantine on cytokine levels in bipolar II depression: a 12-week double-blind, randomized controlled trial. *J. Clin. Psychopharmacol* 34(3), 337-343 (2014).

128. McCloud TL, Caddy C, Jochim J, *et al.* Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. *Cochrane. Database. Syst. Rev* CD011611 (2015).

129. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *J. Clin. Psychiatry* 73(1), 81-86 (2012).

130. Keck PE, Mintz J, McElroy SL, *et al.* Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol. Psychiatry* 60(9), 1020-1022 (2006).

131. Sublette ME, Segal-Isaacson CJ, Cooper TB, *et al.* Validation of a food frequency questionnaire to assess intake of n-3 polyunsaturated fatty acids in subjects with and without major depressive disorder. *J. Am. Diet. Assoc* 111(1), 117-123 (2011).

132. Bauer M, London ED, Rasgon N, *et al.* Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. *Mol. Psychiatry* 10(5), 456-469 (2005).

133. Stamm TJ, Lewitzka U, Sauer C, *et al.* Supraphysiologic doses of levothyroxine as adjunctive therapy in bipolar depression: a randomized, double-blind, placebo-controlled study. *J. Clin. Psychiatry* 75(2), 162-168 (2014).

134. Kanba S, Kato T, Terao T, *et al.* Guideline for treatment of bipolar disorder by the Japanese Society of Mood Disorders, 2012. *Psychiatry. Clin. Neurosci* 67(5), 285-300 (2013).

135. Agosti V and Stewart JW. Efficacy and safety of antidepressant monotherapy in the treatment of bipolar-II depression. *Int. Clin. Psychopharmacol* 22(5), 309-311 (2007).

136. Quitkin FM, Stewart JW, McGrath PJ, *et al.* Columbia atypical depression. A subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. *Br. J. Psychiatry* 21(1), 30-34 (1993).

137. Cohn JB, Collins G, Ashbrook E, *et al.* A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder. *Int. Clin. Psychopharmacol* 4(4), 313-322 (1989).

138. Fogelson DL, Bystritsky A, Pasnau R. Bupropion in the treatment of bipolar disorders: the same old story? *J. Clin. Psychiatry* 53(12), 443-446 (1992).

139. Thase ME, Mallinger AG, McKnight D, *et al.* Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *Am. J. Psychiatry* 149(2), 195-198 (1992).