EXPERT OPINION

Drugs under early investigation for the treatment of bipolar disorder

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Introduction: Despite the availability of several treatment options for bipolar disorder (BD), patients suffer from chronic, subsyndromal symptoms, quite frequent polarity shifts, cognitive impairment and poor community function. Overall, the current treatment outcomes for BD highlight the need to develop targeted, more effective and safe treatments.

Areas covered: This review focuses on compounds currently under investigation for BD, covering compounds tested through animal studies to those in Phase II clinical trials over the past 5 years. These drugs concern all phases of BD treatment, that is, mania, depression, maintenance, and cognitive dysfunction.

Expert opinion: Limitations exist in applying valid preclinical bipolar models and study designs. Research emphasis is given mainly on bipolar depression, with few compounds showing some evidence of efficacy. Non-effectiveness in current studies of mania and maintenance treatment reflects the need for novel compounds. Glycogen synthase kinase 3, casein kinase 1, inositol monophosphatase inhibition, histone deacetylase inhibition pathways are known targets that should proceed from preclinical to the clinical trial level.

Keywords: bipolar disorder, cognitive deficits, drug development, target, treatment

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1. Introduction

Bipolar disorder (BD) is a potentially lifelong and disabling illness characterized by episodes of mania or hypomania and episodes of depressed mood. The peak age of onset is 15 – 19 years and the lifetime prevalence of BD I (mania and depression) is estimated at 1% and BD II (hypomania and depression) at 0.4% of the adult population [1].

Drug treatment of BD is challenging due to its episodic, recurrent and heterogeneous nature. Additional treatment challenges include the relatively high comorbidity of BD with other psychiatric disorders, such as anxiety disorders, substance misuse, personality disorders, attention deficit hyperactivity disorder and eating disorders and also medical comorbidities [2].

Several pharmacological compounds are validated as effective for BD [3]. Generally, polypharmacy (more than one drugs of same or different pharmacological class) is rather common clinical practice in patients with BD, with mood stabilizers being the pharmacological compounds most frequently prescribed [4]. It has been argued that polypharmacy in BD does not seem to contribute to decreased rates of illness chronicity and improved functional outcome [5]. Indeed, evidence from naturalistic studies shows that despite being treated, patients with BD suffer from chronic, subsyndromal symptoms, quite frequent polarity shifts [6,7] and poor community function [8]. Cognitive impairment in BD contributes to the

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Article highlights.

- Lithium remains the gold standard and the key to unlock new pathways for understanding neurobiological mechanisms.
- Glycogen synthase kinase 3, casein kinase 1, inositol monophosphatase inhibition, histone deacetylase inhibition pathways are promising targets for new compounds under current investigation.
- In the past 5-years 'dis'treatable bipolar depression was the focus of research. More emphasis is also needed on cognitive deficits of bipolar disorder (BD). Current not promising results in maintenance and mania treatment may reflect research embarrassment of what is hypothetically known in BD.
- Limitations in valid preclinical models and disorder heterogeneity impose a barrier in developing new compounds for bipolar treatment.
- Scientific rational regarding trial design, bipolar cohort homogeneity should be thoroughly revised.

This box summarises key points contained in the article.

poor functional outcome of the illness and has recently been recognized as a treatment target for BD [9].

Overall, current treatment outcomes of BD highlight the need to develop targeted, more effective and safe treatments. Moreover, diagnostic boundaries of BD are the subject of intense debate [10,11]. For example, patients with major depression plus hypomanic symptoms more closely resemble patients with BD on a number of clinical validators of bipolarity. Therefore, drugs under investigation for the treatment of BD may also be useful for a broader spectrum of mood disorders with subthreshold bipolarity. In this review, we will focus on early investigational compounds tested for mood stabilizing, antimanic, antidepressant and cognitive effects for BD in animal models and Phase II trials in an effort to identify compounds that hold promise for the improvement of treatment outcomes of BD. Phase III and IV drugs were not considered in this review.

2. Methodology and selection criteria

Clinical trials were identified and selected from databases of the National Institutes of Health [12], the European Medicines Agency (EU Clinical Trials Register) [13], World Health Organization (International Clinical Registry Platform) [14] and Center Watch (Center Watch: Clinical Research and Drug Information) [15]. Other resources from medical journals, using PubMed, Scopus and PLOS ONE were also taken into consideration. Studies were accessed between 1st October and 10th November 2014.

Our search criteria concerned BD in adults or elderly patients. Studies in paediatric or adolescent BD were excluded. The primary outcome was at least one of the following: efficacy or safety in bipolar depression, manic symptoms, maintenance treatment or cognitive deficits. Compounds were tested either as monotherapy or adjunctive treatment in all the above conditions. Phase I, II clinical trials and animal studies were included. Phase I or II trials of compounds that were also evaluated in later phase trials were excluded from our search. The clinical trials were recruiting or active (not recruiting), or completed in 2010 or later.

Experimental drugs were classified according to the treatment condition tested and trial phase. Specifications of current clinical trial status (having results, completed, recruiting or ongoing with estimated primary completion date) are also defined.

3. Drugs under early investigation for maintenance treatment

Our search identified seven eligible clinical Phase I or II trials for BD maintenance treatment evaluating seven different developing compounds. Five of them were completed at the time of last assessment, whereas two of them were still ongoing or recruiting patients (**Table 1**).

3.1 Eslicarbazepine acetate (BIA 2-093)

Eslicarbazepine acetate (ESL) is a voltage-gated sodium channel blocker with anticonvulsant activity, recently approved as adjunctive therapy in adults with partial-onset epileptic seizures [16]. A Phase II study evaluated the dose-dependent efficacy, safety and tolerability of ESL recurrence prevention of BD. Eighty-seven patients in this double-blind study were randomized in three dosage groups, taking 300 mg (n = 35), 900 mg (n = 26), or 1800 mg (n = 26) of ESL. Fifty-six out of 87 total subjects across groups (64%) showed no worsening of symptoms according to the Clinical Global Impression – Bipolar Version (CGI-BP) Scale. No statistically significant difference between the ESL dosage groups in the efficacy analysis was found. The compound was found well tolerated with no major safety differences between the groups [17].

3.2 Memantine

Memantine is a known NMDA receptor antagonist approved for moderate to severe Alzheimer's disease treatment and has shown some evidence of efficacy in manic symptoms [18], while also shares possible antidepressant [19] and mood-stabilizing properties [20]. In a 12-week Phase II – III, randomized, double-blind, controlled study in BD II patients undergoing treatment with valproate, memantine was tested for its efficacy as an add-on mood stabilizing treatment. The Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS) were used to evaluate clinical response. There was no significant difference in pre- and post-treatment YMRS and HDRS scores between the valproate plus memantine and valproate plus placebo groups [21].

Table 1. Compounds under early clinical investigation for maintenance treatment in bipolar disorder.

Compound	Identifier	Phase	Treatment As	Status	Results
Eslicarbazepine acetate	NCT01825837	Phase II	Monotherapy	Completed	No significant dose-related differences in CGI-BP
Memantine	NCT01188148	Phase II – III	Add-on	Completed	No significant differences versus placebo in YMRS and HDRS
Cytidine and ω-3 fatty acids	NCT00854737	Phase II	Add-on	Completed	Not superior to Placebo
Pregabaline	Open label	Phase II	Add-on	Completed	Improvement in CGI-BP
Taurine	NCT00217165	Phase II	Add-on	Completed	No results available
Digibind (Fab)	NCT00550576	Phase II	Add-on	Completed	No results available
Inositol hexaphosphate (IP6)	NCT02081287	Phase I	Add-on	Active, not recruiting	November 2015
ELND005	NCT01674010	Phase II	Add-on	Active, not recruiting	September 2015

CGI-BP: Clinical Global Impression - Bipolar Version; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale.

3.3 ω-3 fatty acids, alone or in combination with cytidine

Previous studies examining the role of nutritional supplements, mainly ω-3 fatty acids (O3FA), in BD offered good evidence of its efficacy as an adjunctive treatment in bipolar depression but not for attenuating manic symptoms [22]. Moreover, cytidine, which is necessary to form key intermediates in the biosynthesis of phospholipids in cell membranes, has shown antidepressant-like effects in animal models [23] and in bipolar patients [24]. In a 4-month, Phase II, randomized, double-blind, placebo-controlled pilot study a combination of cytidine and O3FA was administered. Ninety subjects with BD were assigned to one of three groups taking as add-on treatment: i) O3FA plus cytidine; ii) O3FA placebo; and iii) placebo plus placebo. No differences between the three groups were found in study retention (i.e., the duration of participation until a change in medication due to a mood episode was required). Moreover, there was no significant improvement in mood symptoms measured by YMRS and Montgomery-Asberg Depression Rating Scale (MADRS), neither under O3FA plus cytidine nor under O3FA alone compared to placebo [25]. However, previous studies supported a possible therapeutic role of O3FA in relapse prevention of BD [22,26].

3.4 Pregabalin

Pregabalin is a known antiepileptic drug, which binds to the α-2-delta subunit of the voltage-dependent calcium channel. In an open label observational study, acute and maintenance efficacy of pregabalin as an adjunctive medication for a group of 58 treatment refractory BD patients was evaluated. Mood state before and after initiation of pregabalin was compared using the CGI-BP. Patients were assessed for acute response in two-month time and for maintenance treatment in 3 years' time. In 41% of the patients that were rated as acute responders, pregabalin produced either mood stabilizing (in 50%), antidepressant (in 29%), or antimanic (in 21%) effect. The average dose for the acute responders was 72 ± 69 mg/d. Intolerable side-effects were the most common reason for a failed acute trial of pregabalin (79% of the non-responders). Ten (42%) of the acute responders were still taking pregabalin as adjunctive treatment at follow-up [27]. The results of this open study suggest that pregabalin may be a safe and effective acute and maintenance adjunctive treatment for BD patients.

3.5 Ongoing trials for maintenance treatment

3.5.1 Taurine

Taurine is a conditional amino acid that is considered to have antidepressant properties [28] and some actions similar to mood stabilizers [29]. However, controlled studies examining the mood effects of taurine are limited. In a current Phase II follow-up study, taurine's effects on mood stability and manic symptoms in BD are examined. This study has been completed, but no results had been announced at the time of writing.

3.5.2 Antibodies to digoxin

Digoxin immune (Fab) is used as an antidote for digoxin toxicity. Endogenous digitalis-like compounds in the brain have been implicated in the pathogenesis of mood disorders [30]. An open Phase II study, in bipolar patients receiving maintenance treatment, tested the efficacy of administration of one intravenously dose of digoxin antibodies. Outcome measures and results of the study are not provided.

3.5.3 Inositol hexaphosphate

Inositol hexaphosphate (IP6) is a natural carbohydrate molecule present in most plant and animal cells and as a form of inositol naturally occurs from phosphorylation of myo-inositol. There is evidence for its therapeutic role in depression [31], whereas there is only a trend of efficacy by previous studies in bipolar depression [32,33]. In a still active, Phase I, pilot trial in 30 bipolar subjects IP6 will be assessed regarding its efficacy and tolerability as an adjunctive treatment to lithium and compared to lamotrigine.

Table 2. Compounds under early clinical investigation for the treatment of manic episodes.

Compound	Identifier	Phase	Treatment as	Status	Results
Eslicarbazepine Acetate	NCT01822678	Phase II	Monotherapy	Completed	No significant change in YMRS
Pentazocine	NCT00431184 NCT00125931	Phase II	Monotherapy	Completed	Significant improvement in MACS
Memantine	NCT00106405	Phase II	Monotherapy	Completed	No results available
Lovastatin	IRCT201302203930N18	Phase II – III	Add-on	Completed	No significant difference versus placebo
Celecoxib	IRCT201307171556N53	Phase II – III	Add-on	Recruiting	September 2015

MACS: Mania Acute Rating Scale; YMRS: Young Mania Rating Scale.

3.5.4 *ELND005*

ELND005, also known as scyllo-inositol, is an amyloid β peptide aggregation inhibitor under investigation for Alzheimer's disease [34]. A Phase II, randomized, double-blind, placebo-controlled study has begun in 400 bipolar patients with primary aim to determine whether ELND005 is effective in the maintenance treatment of BD I, when added to other therapies. Results from this study are expected in 2015.

4. Drugs under early investigation for the treatment of manic episodes

Our search identified six eligible clinical trials for manic episode treatment evaluating five different developing compounds. Five trials were completed at the time of last assessment, whereas one is currently recruiting subjects (**Table 2**).

4.1 Eslicarbazepine acetate

In a Phase II, double-blind, randomised, placebo-controlled dose-titration study ESL was tested as an antimanic agent in 160 BD patients experiencing an acute manic (including mixed) episode. Patients were randomized to dose titration groups: i) ESL 1800 mg; ii) ESL 2400 mg; and iii) placebo 1 – 3 tablets. ESL was up-titrated 3 and 6 days after initiation and maximum dose was kept for up to 3 weeks. Efficacy analysis revealed a trend of greater improvement in YMRS in ESL 2400 mg group versus placebo, but not statistical significance [35]. Both the ESL groups showed a comparably good safety profile. More common adverse effects were headache, dizziness, nausea, vomiting and diarrhoea.

4.2 Pentazocine

Pentazocine is a kappa agonist and mixed mu agonist frequently used for pain control. The opiate neurotransmitter system is thought to be involved in many abnormal mood states, including manic symptoms [36]. Two Phase II studies in BD patient in a manic episode, one open-label and one double-blind versus lorazepam, evaluated acute antimanic effects of pentazocine (in combination with Naloxone, which is not orally bioavailable). In ten subjects who participated in the open label group, manic symptoms were reduced 6 h after administration. Pentazocine had a statistically significant effect on acute manic symptoms rated with Mania Acute Change Scale (MACS) [37]. Nevertheless, in the double-blind study with 19 participants and cross-over design, pentazocine (100 mg/d) did not significantly differ from lorazepam (0.5 mg/d) in a mixed model analysis regarding manic symptoms measured by MACS, 5 h after drug administration [38]. Pentazocine was well tolerated and safe.

4.3 Lovastatin

Lovastatin a statin used for the treatment of dyslipidemia and the prevention of cardiovascular disease might also share antidepressant properties [39]. In a randomized, double-blind, placebo-controlled, Phase II – III clinical trial examining the efficacy and safety of lovastatin as an adjuvant for treating manic episodes, 60 BD patients were randomly allocated into either the two groups, taking lovastatin (up to 40 mg/day) or placebo. Lovastatin in combination with lithium was well tolerated, but no significant difference from placebo was found regarding its efficacy. Results supported that lovastatin as an adjuvant treatment to lithium did not have any effect in the acute phase of mania [40].

4.4 Ongoing trials for the treatment of manic episodes

4.4.1 *Memantine*

Memantine has shown antimanic properties in animal models [41]. Its safety and efficacy in bipolar patients hospitalized for mania was evaluated in an open-label, Phase II study. Previously reported results indicated improvement in manic symptoms measured by YMRS and Mania Rating Scale in a dosage range of 20 – 30 mg/d. Although all patients in this study had good response after 21 days [18], the high frequency of adverse events raises question upon memantine's tolerability in manic bipolar patients. Final results are yet to be determined.

4.4.2 *Celecoxib*

Celecoxib is a COX-2 selective nonsteroidal anti-inflammatory drug, which is considered to be an effective add-on treatment for unipolar depressive patients [42]. An ongoing Phase

Table 3. Compounds under early clinical investigation for the treatment of bipolar depression.

Compound	Identifier	Phase	Treatment as	Status	Results
Cariprazine	NCT01396447	Phase II	Monotherapy	Completed	Improvement in MADRS, CGI–S
	NCT00852202				
Riluzole	NCT00544544	Phase II	Monotherapy	Completed	Significant reduction in HDRS
	NCT00054704		Monotherapy	Recruiting	January 2015
	NCT00376220		Monotherapy	Completed	No results available
Levothyroxine	NCT01528839	Phase II – III	Add-on	Completed	No statistical difference versus placebo
Acetyl-l-carnitine plus α-lipoic	NCT00719706	Phase II	Add-on	Completed	No statistical difference versus placebo
Agomelatine	Open label	Phase II	Add-on	Completed	Improvement in HDRS-17
N-acetyl cysteine	ACTRN12607000074493	Phase II	Add-on	Completed	Improvement in BDRS
	NCT01797575		Add-on	Recruiting	June 2015
(and Aspirin)	NCT02294591		Add-on	Recruiting	October 2016
Uridine	NCT00812058	Phase II	Monotherapy	Completed	No results available
AZD4451	NCT01196676	Phase I	Monotherapy	Completed	No results available
LY2979165	NCT01383967	Phase I	Monotherapy	Completed	No results available
	NCT01248052				
Asenapine	NCT01807741	Phase II	Monotherapy	Recruiting	July 2015
Isradipine	NCT01784666	Phase II	Add-on	Recruiting	February 2015
Simvastatin	NCT01665950	Phase II	Add-on	Recruiting	January 2017
Align	NCT02155972	Phase II	Add-on	Recruiting	January 2015

BDRS: Bipolar Depression Rating Scale; CGI-S: Clinical Global Impression-Severity; HDRS-17: Hamilton Depression Rating Scale-17 item; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating.

II – III double-blind, placebo-controlled trial aims at assessing the efficacy of celecoxib as an adjuvant agent in the treatment of manic episode. Results are expected at September 2015 [43].

5. Drugs under early investigation for the treatment of bipolar depression

Our search identified 18 eligible clinical trials for the treatment of bipolar depression corresponding to 13 different developing compounds. Eleven trials were completed at the time of last assessment, whereas seven are currently recruiting subjects (**Table 3**).

5.1 Cariprazine

Cariprazine is a novel potent dopamine D_3-preferring D_3/D_2 receptor partial agonist that has being tested in late-stage clinical studies for bipolar manic/mixed episodes with good efficacy results so far [44]. At the same time, two Phase II, randomized, double-blind, placebo controlled trials for efficacy, safety and tolerability of cariprazine in bipolar depression were recently completed. Sponsor has recently announced initial results of one study [45], in which 584 patients were randomized in four treatment groups: cariprazine 0.75 mg/day, 1.5 mg/day, 3.0 mg/day, and placebo. Statistically significant improvements were observed in the cariprazine 1.5 mg/day group compared to placebo at 6 weeks in the MADRS and the Clinical Global Impressions – Severity (CGI-S). Akathisia and insomnia were the most common adverse events (incidence ≥ 10% and greater than placebo), regardless of the dosage group.

5.2 Riluzole

Riluzole is a sodium channel antagonist approved for amyotrophic lateral sclerosis. A previous small open label with 14 bipolar depressed patients found that riluzole used adjunctively to lithium for six weeks demonstrated antidepressant efficacy [46]. Recently, in an open-label trial riluzole was administered 100 – 200 mg daily for 6 weeks to 14 patients with bipolar depression and showed significant reduction of HDRS score [47]. Two other double-blind, placebo-controlled trial studies of riluzole in bipolar depression, one recently completed and one still ongoing, will give more results concerning riluzole's antidepressant properties.

5.3 Levothyroxine

Thyroid axis dysfunction may contribute to the pathophysiology of BD [48]. A Phase II – III, randomized, placebo-controlled trial recently evaluated the efficacy and safety of add-on treatment with levothyroxine (300 μg/d) in combination with mood stabilizer/antidepressant therapy in bipolar depression patients. In this 6 week study in 74 patients, mean change in the HDRS score was assessed in the levothyroxine group compared to the placebo group. Results indicated that the course of HDRS scores over time from randomization to week 6 was significantly different between groups at week 4 ($p = 0.046$) but not at the end of the trial ($p = 0.198$) [49].

5.4 Acetyl-L-carnitine and α-lipoic acid

Acetyl-L-carnitine (ALCAR) and α-lipoic acid (ALA) are known mitochondrial enhancers. They have been recently evaluated as an augmentation treatment compared to placebo in bipolar depressed patients, who display an incomplete response to conventional treatments. In a 15-week, Phase II, placebo-controlled, double-blind study, 20 patients were administered with ALCAR at 1000 – 3000 mg/day and ALA at 600 – 1800 mg/day and were compared to 20 patients that received placebo in terms of their symptom improvement measured with HDRS, MADRS, YMRS, and Clinical Global Impression-Severity and Improvement (CGI-S and CGI-I). No significant difference between ALCAR/ALA and placebo group was found on change from baseline in any outcome measure in both the longitudinal and last-observation-carried-forward analyses [50].

5.5 Agomelatin

Agomelatin is a melatonin receptor agonist (MT_1 and MT_2) and a 5-HT_{2C} receptor antagonist approved for the treatment of major depression. Nevertheless, little evidence exists on its efficacy in bipolar depression. A recently published open-label study, in a 6 week open parallel-group design, assessed the efficacy of agomelatine as an adjunct to valproate or lithium in the treatment of a BD II acute depressive episode. No blind assessment or placebo controls were adopted. Response was defined as > 50% decrease in depressive symptom severity from the baseline HDRS-17 score. Eighteen out of 28 enrolled patients (64%) showed response after 6 weeks (primary study endpoint), whereas 24 (86%) responded by 36 weeks (end of trial) as demonstrated by intend to treat analysis. Two drop-outs due to hypomanic symptomatology emergence were noted [51].

5.6 *N*-acetylcysteine

N-acetylcysteine (NAC) is a glutathione precursor with neuroprotective effects that is considered a nutritional supplement. A previous double-blind placebo-controlled trial offered support to its possible therapeutic role in depressive symptoms in BD [52]. More recently, in a large open-label study 149 BD patients in moderate depression received NAC 1 g/d as an add-on treatment for 8-week. A significant improvement in depressive symptoms as measured by the Bipolar Depression Rating Scale was found as well as improvement in patients' functioning and quality of life [53]. Two ongoing Phase II, double-blind, placebo-controlled studies will further evaluate NAC's efficacy (alone or in combination with aspirin) as an add-on treatment in bipolar depression.

5.7 Ongoing trials for the treatment of bipolar depression

5.7.1 *Uridine*

Uridine is part of a family of compounds called pyrimidines and in particular, a ribosylated uracil, a pyrimidine required for RNA synthesis and important for mitochondrial function. Early studies (before 2008) demonstrated favourable results for uridine in bipolar depression [54]. A Phase II randomized, double-blind, placebo-controlled study to assess the safety, tolerability and efficacy of RG2417 (oral Uridine) in the treatment of bipolar I depression has recently been completed but its results are not available at present.

5.7.2 *AZD4451*

AZD4451 is a novel compound being tested in a Phase I, randomized, double-blind, placebo-controlled trial for bipolar depression regarding its safety, tolerability and pharmacokinetics properties.

5.7.3 *LY2979165*

This compound is an mGlu2 agonist that is presumed to have antidepressant properties. Two Phase I, double-blind, safety studies of LY2979165 is being performed in healthy subjects and results are expected.

5.7.4 *Asenapine*

Asenapine is a known atypical antipsychotic, recently approved for the treatment of schizophrenia and acute mania. In September 2013 a Phase II, double-blind, placebo-controlled trial was initiated in 86 bipolar depressed patients in order to evaluate the efficacy of asenapine (at 5 – 10 mg/d) versus placebo in bipolar depression [55].

5.7.5 *Isradipine*

Isradipine, a dihydropyridine-class calcium channel antagonist is used to treat high blood pressure. A Phase II, randomized, placebo-controlled trial is currently recruiting participants, aiming primary at estimating the antidepressant efficacy of isradipine versus placebo as an adjunct to lithium, valproate or atypical antipsychotics among individuals with BD I in a nonpsychotic major depressive episode. Recently, a pilot, 8-week investigation of isradipine in patients with bipolar depression demonstrated a favourable antidepressant result assessed with MADRS; however the sample completed the trial was very small (only two subjects) [56].

5.7.6 *Simvastatin*

Simvastatin is a statin used to treat dyslipidemia. According to the inflammatory hypothesis of depression, it has been proposed that drugs with an anti-inflammatory action, such as simvastatin, could be useful in some depressive patients [57]. However, the findings from clinical studies on the association between statins and depressive symptoms have been conflicting [58]. An ongoing, Phase II, double-blind, placebo-controlled trial aims at estimating the antidepressant efficacy of simvastatin versus placebo as an adjunct to lithium, valproate, and other atypical antipsychotic among individuals with BD I in a nonpsychotic major depressive episode.

Table 4. Compounds under early clinical investigation for the treatment of cognitive deficits in bipolar disorder.

Compound	Identifier	Phase	Status	Results
Erythropoietin	NCT00916552	Phase II	Completed	Improvement in SA, EFR, IP
Mifepristone	ISRCTN27649427	Phase II	Completed	Improvement in SWM
Methylphenidate	NCT0202020	Not specified	Not yet open	December 2014

EFR: Emotional face recognition; IP: Information processing; SA: Sustained attention; SWM: Spatial working memory.

5.7.7 Align

Align stands for the dietary supplement of bifidobacterium infantis, a stomach probiotic. Previous studies indicated that probiotics may improve mood and anxiety symptoms [59,60]. An ongoing 8-week randomized, double-blind, placebo-controlled study assesses Align as an add-on treatment in bipolar depression.

6. Drugs under early investigation for the treatment of cognitive deficits in BD

Our search identified three Phase II, eligible clinical trials for cognitive enhancement treatment in BD corresponding to three different developing compounds (**Table 4**).

6.1 Erythropoietin

Erythropoietin is involved in brain repair and may be a candidate for future treatment strategies in mood disorders and especially in the treatment of coexisting cognitive deficits [61]. In a double-blind, placebo-controlled study 44 patients were randomized in two groups, given weekly either erythropoietin (40,000 IU) or saline (sodium chloride [NaCl] 0.9%) infusions for 8 weeks. Erythropoietin significantly enhanced sustained attention, recognition of happy faces, and speed of complex information processing. These effects occurred in the absence of changes in simple reaction times and were maintained after red blood cell normalization. There was no significant changes in other cognitive domains examined, namely verbal memory and learning, verbal fluency, psychomotor speed and executive functions, as well as in measures of mood [62].

6.2 Mifepristone

Mifepristone is a progesterone antagonist and a glucocorticoid receptor antagonist that may reduce hyperactivity of the hypothalamic-pituitary-adrenal axis at high doses. Earlier studies have reported a favourable effect of mifepristone in bipolar depression [63]. Mifepristone's efficacy was assessed as an adjunctive treatment (at 600 mg/day) for one week in a placebo-controlled, double-blind trial in 60 patients with bipolar depression. Mifepristone treatment was associated with significant improvement in spatial working memory (SWM), which was the primary outcome measure, but not in other cognitive domains examined (attention, memory, executive functions). Improvement in SWM performance remained 7 weeks after treatment's cessation, was predicted by cortisol response and occurred in the absence of an improvement in depressed mood [64].

6.3 Methylphenidate

Methylphenidate is a psychostimulant drug used mainly for the treatment of attention-deficit hyperactivity disorder (ADHD). It is acting primarily by blocking the dopamine and norepinephrine transporter leading to increased concentration. Methylphenidate is under investigation as an antimanic agent in a multicenter study, based on the 'vigilance regulation model of mania' hypothesis [65], whereas its therapeutic role as an adjunctive in bipolar depression has been better studied [66]. Although it is usually prescribed as cognitive enhancer in a broad range of mental disorders, especially in young patients, there are no studies on its efficacy for cognitive deficits in BD. Currently, an ongoing trial with crossover design in 40 patients aims at exploring the effect of methylphenidate on working memory, attention and decision making in adults with BD in remission or in depressed state in comparison to healthy adults and adults with ADHD.

7. Evidence from animal studies

Our search identified seven eligible animal studies on developing compounds in BD that had published results from 2010 to 2014 (**Table 5**). Developing an animal model for BD is extremely challenging at the moment, so we considered only studies for mania models or compounds tested on both mania and depression models, excluding thus compounds tested solely for depression animal models.

7.1 CK01

CK01 is an inhibitor of casein kinase 1 (CK1) ε/δ. CK is a critical protein involved in the regulation of molecular and thus of circadian rhythms, which are disrupted in BD, especially in mania. CK01 is similar to PF-670462 that inhibits the activity of CK1, which has been found that normalizes amphetamine-induced hyperactivity in mice and stabilizes rhythms in arrhythmic animals [67]. CK01 was tested and compared to lithium administration in CLOCK mice, which have a mutation in one of the central circadian proteins and display severely disrupted rhythms along with a behavioural profile that closely resembles human mania (hyperactivity, decreased anxiety, that is, increased exploratory drive, decreased depression-like behaviour, hyperhedonic response to rewarding stimuli). Administration of CK01 resulted to a

Table 5. Emerging compounds in animal studies for the treatment of bipolar disorders.

Compound	Pathway	Clinical effect	Ref.
CK01	CK1ε/δ inhibition	Reversal of the anxiety-related behaviour, partial reversal of the depression-related phenotypes of the Clock mutant mouse	[61]
Ebselen	IMPase inhibition	Induces lithium-like effects on mouse behaviour of rearing and amphetamine-induced hyperactivity	[63]
TAT - KLCpCDK peptide	GSK-3β inhibition of KLC2 phosphorylation	Antimanic-like and antidepressant-like effects in animal models	[66]
GSK 3β-compound 3a	Highly selective GSK-3β inhibitor	Locomotor activity attenuation in the d-AMPH[f] + CDP[g] -induced hyperactivity model	[74]
Cpd-60	HDAC 1/2 inhibition	Attenuated locomotor activity following acute AMPH challenge, decreased immobility in the forced swim test in mice	[67]
Sodium butyrate (SB)	HDAC inhibitor	Reversal and prevention of d-AMPH-induced behavioural effects in Wistar rats	[68-70]
Retigabine, ICA-27243	Kv7 channel activation	Antimanic effects in d-AMPH + CDP mouse mania model	[77]

CK: Casein kinase; CPD: Chlordiazepoxide; d-AMPH: D-amphetamine; GSK-3: Glycogen synthase kinase 3; HDAC: Histone deacetylase; IMPase: Inositol monophosphatase; KLC2: Kinesin light chain 2.

reversal of the anxiety-related behaviour (similar to lithium), and partial reversal of the depression-related phenotypes (unlike lithium, which normalizes the effects on depression-related behaviour by causing an increase in total immobility time) [68]. This positive result suggests that CK1ε/δ inhibitors may be effective compounds for rhythm and mood stabilization in BD.

7.2 Ebselen

Ebselen (also called PZ 51 or DR3305) is a mimic of glutathione peroxidase possibly acting as an inositol monophosphatase inhibitor. Inositol monophosphatase inhibition (IMP) is supported to be an important, though equivocal, lithium's therapeutic target in BD. Ebselen has exhibited lithium-like effects in both mice depression models [69] and lithium-sensitive mouse models of mania [70].

7.3 TAT-KLCpCDK

Glycogen synthase kinase 3 (GSK-3) is a potential target for drug development in BD [71], as lithium inhibits GSK-3 and lithium and other GSK-3 inhibitors demonstrate both antimanic-like and antidepressant-like efficacy in animal models of mood-associated behaviours, particularly in the amphetamine-induced locomotion and forced swim tests [72,73]. A recent animal study has suggested that GSK-3 phosphorylation of kinesin light chain 2 (KLC2) leads to the dissociation of AMPA-containing vesicles from the kinesin cargo system. The peptide Tyrosine Aminotransferase (TAT)-KLCpCDK is a specific inhibitor for KLC2 phosphorylation by GSK-3β. TAT-KLCpCDK demonstrated antimanic and antidepressant-like effects similar to lithium's on amphetamine-induced hyperactivity and in the tail suspension and forced swim tests, which are commonly used animal models of mania and depression respectively. This trial suggested that KLC2 may be a cellular target of GSK-3β capable of regulating particularly AMPA receptor trafficking, as well as mood-associated behaviours in animal models [74].

7.4 GSK 3β - compound 3a

Another GSK-3 inhibitor produced for the manipulation of the GSK-3-signaling cascade produces with implicating antimanic effects is compound 3a, a pyrazolone highly selective for GSK. In animal trials of mania (chlordiazepoxide/amphetamine-induced hyperactivity) model, GSK 3β - Compound 3a showed properties of neuroprotection in the homocysteic acid model of oxidative stress and antimanic effects by reducing locomotor activity in tested rats [75]. Moreover, previous studies in Black Swiss mice with amphetamine-induced hyperactivity that tested other GSK3 inhibitors provided some evidence for their antimanic efficacy [76].

7.5 Cpd-60

Compound 60 (Cpd-60) is an inhibitor of the class I histone deacetylase (HDAC) family members, HDAC1 and HDAC2. Cpd-60 treatment was tested for 1 week in established mice models for both mania (following acute amphetamine challenge) and depression (forced swim test) and was associated with attenuated locomotor activity and decreased immobility, respectively. These behavioural changes were related with gene expression alteration, as confirmed by increased histone acetylation. Results of this study provide evidence that selective inhibition of HDAC1 and HDAC2 in brain may be a candidate epigenetic-based target for developing treatments for BD [77].

7.6 Sodium butyrate

Sodium butyrate (SB) is another HDAC inhibitor. Animal studies in preclinical models of mania and depression

reinforce the hypothesis of its treatment role in BD. SB was investigated in rats submitted to an animal model of mania induced by d-amphetamine (d-AMPH). Results of two studies showed that SB reversed and prevented d-AMPH-induced behavioural effects (i.e., locomotor activity and risk-taking behaviour) [78,79]. Similarly, a study compared SB to lithium and valproate found that all compounds managed partial reversal of HDAC and reversal of AMPH-induced hyperactivity in Wistar rats [80]. Another study evaluating the behavioural effects of SB in animal models of depression and mania, demonstrated reversal of depressive-like and manic-like behaviours, implicating a possible mood stabilizing role [81]. Furthermore, trials in mice models of depression (maternal deprivation and chronic mild stress) indicate that SB treatment improved the recognition memory and reversed the neurotrophins levels decreased in the hippocampus [82].

7.7 Retigabine and ICA-27243

Pharmacological stimulation of voltage-dependent potassium Kv7 channel function has shown anti-manic such as efficacy in the D-amphetamine and chlordiazepoxide (AMPH + CDP) induced hyperactivity model of mania [83]. In a recent study, administration of the Kv7 channel modulators, that is, retigabine (an antiepileptic acting as Kv7.2-Kv7.5 channel opener) and ICA-27243 (enhances the activation of KCNQ2/3 channels and exhibits anticonvulsant efficacy in pre-clinical models) reduced brain metabolic activity similarly to the effect of mood stabilizers, lithium and valproate, in an AMPH + CDP mania model. Moreover, both compounds showed increased phosphoserine-9 levels of GSK3b in the prefrontal cortex and hippocampus, a common molecular mechanism shared by anti-manic drugs. These data emphasize the potential of Kv7 channel openers in the treatment of BD and suggest that Kv7.2/Kv7.3 channels may present a novel anti-manic therapeutic target [84].

8. Needs, limitations and future perspectives in investigation of drug development for BD

BD presents clinicians with a major treatment challenge: it has a highly heterogeneous presentation and course (bipolar type I, II, rapid cycling, with mixed or psychotic features), which currently remain poorly predictable [85]; treatment response is variable and euthymic patients in the maintenance phase frequently experience residual mood symptoms, cognitive impairment and suboptimal functioning [86]. As an oxymoron as it may sound, combination treatments or polypharmacy especially during maintenance phase is currently the 'only choice', as recent meta-analytic evidence has shown that no monotherapy for the maintenance phase is associated with a significantly reduced risk for manic and depressed relapses [87]. Poor adherence of patients to treatment adds to the complexity of management of BD, with adherence rates as low as 35% [88]. The above highlights the need for new, targeted, effective and safe treatments for BD.

Beyond the 'classic' routes, such as dopamine, serotonin neurotransmission, novel extra- and intra-cellular pathways implicated in the pathogenesis of BD are explored and a great number of compounds acting on novel therapeutics targets are tested [89,90]. Our search detected a large number of compounds under early investigation for the treatment of BD but a rather small number of studies with promising results.

8.1 Maintenance treatment

No currently investigated drug showed efficacy for recurrence prevention. Surprisingly, the antiepileptic eslicarbazepine was not effective as monotherapy, whereas pregabalin might be useful as add-on treatment but this have to be confirmed by double-blind controlled trials. Neither the NMDA-antagonist memantine nor O3FA were found to be effective as add-on treatments, although both share neuroprotective and neurotrophic properties [91,92].

Research has recently focused on GSK-3-specific-mediated compounds, as it is known that therapeutic targets of lithium and other mood stabilizing drugs involve the GSK-3 [93], but also mediators of phosphoinositide pathway and HDACs [90]. GSK-3 inhibitors have shown promising results in preclinical models of both mania and depression. Developing high selective compounds, such as TAT-KLCpCDK peptide and GSK 3β - Compound 3a, might be promising. Concerning phosphoinositol pathway, ebselen represents a lithium mimetic expected to move forward to clinical trials [70]. The epigenetic approach of selective inhibition of HDAC in brain may be a candidate pathway for developing mood disorders treatments and expectations on Cpd-60 and SB in terms of safety and efficacy are growing. Finally, as circadian rhythm preservation is crucial in bipolar prophylaxis, CK1 inhibitor CK01 seems worth of further evaluating, whereas another drug for disrupted circadian rhythms, TAK-375SL_301, an ML-1-selective melatonin receptor agonist, has shown efficacy and moved to Phase III studies [94].

8.2 Treatment of manic episodes

Only pentazocine presented positive results in manic episodes, but as the sample size was limited and effectiveness was found to be equal to low-dose lorazepam, skepticism is raised regarding its perspective. New antiepileptics are also tested; eslicarbazepine did not initially showed efficacy, although its relative compound licarbazepine has moved to Phase IV. Antimanic effects of compounds tested on animal models in terms of GSK-3, HDAC inhibition (i.e., ebselen, GSK 3β - Compound 3a, SB), are yet to be evaluated in clinical studies. Of note, there is a lack of early tested anti-dopaminergic compounds, whereas cariprazine has shown efficacy in Phase II and moved to Phase III [95].

8.3 Treatment of bipolar depression

Our study detected 19 early phase trials on potential treatments for bipolar depression. The novel antipsychotic cariprazine has demonstrated promising results and may follow recent

approved antipsychotics quetiapine, lurasidone in bipolar depression treatment, whereas asenapine is under evaluation. There is also some evidence on the efficacy of *N*-Acetyl Cysteine as an add-on treatment in bipolar depression whereas the compound is further tested in double-blind placebo-controlled trials. Agomelatin is expected to proceed to late trial evaluation along with the other melatonin agonist TAK-375SL_301.

On the other hand, even if thyroid hormones are considered as augmenting strategy, levothyroxine did not show efficacy. In the same way, mitochondrial enhancers ALCA and ALA were not superior to placebo, as an add-on treatment, whereas similar acting uridine showed in the past promising results. Another interesting compound is sodium channel antagonist and glutamate reuptake enhancer (by increasing AMPA trafficking) riluzole, which has shown efficacy as monotherapy, though in a small clinical sample. Similar acting isradipine is currently assessed.

8.4 Treatment of cognitive deficits in BD

No pharmacological agent seems so far efficacious for the treatment of cognitive deficits in BD. A number of agents have been tested with mixed results [96]. Our study met two promising compounds, erythropoietin with implicating neurotrophic properties and mifepristone with neuro-antinflammatory action. Methylphenidate may be effective for cognitive symptoms, but risk of mania induction should be clarified. Other agents currently evaluated in later phase trials include the NMDA receptor antagonist memantine, the dopaminergic-acting pramipexole and lurasidone, modafinil, the reversible cholinesterase inhibitor galantamine, insulin and pregnenolone.

9. Conclusion

We reviewed 35 studies corresponding to 29 different compounds under early investigation for BD treatment from 2010 to time of writing. Some of these compounds are new, whereas others are familiar in psychiatry therapeutics or in treatment of somatic diseases. The majority of trials concerned treatment of bipolar depression and only a few examined maintenance or mania treatment, whereas therapeutic options for cognitive dysfunction in BD are emerging. None of the above early investigated compounds was found with hard evidence of efficacy for maintenance and mania treatment. In bipolar depression treatment cariprazine and riluzole show promise. In cognitive dysfunction more studies are needed in order to ascertain erythropoietin's and mifepristone's therapeutic role. Preclinical studies emphasize on GSK-3, CK1, IMP, HDAC inhibition pathways as potential BD treatment targets.

10. Expert opinion

BD is challenging for clinicians. Treatment is always individualized and phase-specific. Drugs currently used for BD are not optimal for many patients. Current unmet needs in the management of BD, that is, poor long-term functional outcome, high rates of residual symptoms, mainly depressive and cognitive, and high comorbidity, highlight the urgent need for developing targeted, more efficacious and safer drugs.

Limited knowledge of the main disease mechanisms has hindered drug development in BD so far. New drugs for BD have been produced as minor variations of older drugs whereas no new class of psychotropic drugs has been developed for several decades. However, during the last decade, significant progress in the knowledge of underlying neurobiological mechanisms implicated in BD has been achieved, mainly through research on molecular targets of lithium and other mood stabilizers. Thus, besides 'traditional' targets, a great number of compounds acting on novel therapeutics targets are currently under early investigation.

New anticonvulsant and antipsychotic agents may enhance treatment options, although the 'traditional' targets in general appear to show limited promise for BD maintenance and mania treatment. On the other hand, among the potential new drugs investigated so far, only a few compounds have shown efficacy in bipolar depression, whereas none has shown the positive effect in maintenance or mania treatment as yet. Results of many Phase II studies with novel compounds are awaited in the near future and the findings from animal studies indicate promising targets of mood stabilizing drugs involving the GSK-3b, IMPase, HDACs and other pathways. Deeper insight into pathophysiological mechanisms of BD, such as neural regulations and cascade of intra-cellular processes, will allow opening novel routes to identification of new potential therapeutic approaches in the future.

However, in these novel routes to drug development for BD methodological difficulties can be spotted. Despite the fact that animal studies may provide a better understanding of the neurobiology of mood disorders and are critical for the future development of new and effective treatments [89,97], reliable, specific and objective models for BD are lacking. It is doubtful, whether behavioural phenotypes of mania or depression reflect BD. Clinical studies design should pay attention on safety principles of each candidate compound and methodological issues regarding intervention (monotherapy or add-on treatment), inclusion criteria (e.g., definition of illness phase and baseline symptom severity), duration of follow-up, sample sizes and outcome measures. Moreover, due to the heterogeneity of BD a number of stratification issues may be crucial for the discovery of therapeutically relevant drugs. For example, possible differences in therapeutic response between women and men [98] or between patients at different stages of the disease [99] and between non-comorbid patients usually included in trials and patients seen in everyday clinical practice [100] should be systematically tested. Not accounting for these potential biases might result in non-reproducible results or a missed opportunity to discover useful drugs.

Cognitive dysfunction in BD is a special area of interest for a number of reasons: it has significant negative impact on functional outcome, current treatments do not have any notable pro-cognitive effects, and our knowledge of specific underlying mechanisms is scarce. Therefore, improving cognition in BD is an important unmet need and more studies are warranted to develop novel therapeutic compounds. The number of existing cognitive enhancers to be tested for this indication is limited. Novel, targeted drugs, such as compounds with neurotrophic or neuro-antinflammatory action, seem to be the most promising option. It is also highly possible that different medication classes may improve different domains of cognitive function.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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