Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Potential novel treatments for bipolar depression

Carlos A. Zarate Jr and Husseini K. Manji

Laboratory of Molecular Pathophysiology & Experimental Therapeutics, Mood and Anxiety Disorders Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Existing pharmacological treatments for bipolar disorder (BPD), a severe recurrent mood disorder, is in general insufficient for many patients. Despite adequate doses and treatment duration, many individuals afflicted with this disease continue to experience mood episode relapses, residual symptoms, and functional impairment. In contrast to the manic phase of the illness where a fairly large variety of effective treatments are available, in bipolar depression effective therapeutics are scarce. This is especially troubling because the long-term course of BPD is dominated by recurrent depressive episodes and lingering depressive symptoms rather than hypomanic/manic episodes. Novel therapeutics – that is, drugs that do not include the existing antipsychotic, antiepileptic, and antidepressant medications – currently being studied to determine their efficacy and safety in bipolar depression include modafinil, pramipexole, N-acetyl cysteine (NAC), scopolamine, agomelatine, riluzole, memantine, ketamine, AMPA potentiators, ketoconazole, mifepristone, celecoxib, creatine, and uridine RG2417. Further study of these drugs will investigate their clinical utility in bipolar depression, and further our understanding of relevant drug targets.

Introduction

Previous chapters of this volume explored the epidemiology, definition, classification, outcome, and currently used pharmacological treatments for bipolar depression. However, it is becoming increasingly clear that current pharmacotherapies are insufficient for many patients with bipolar depression. For instance, a large-scale study funded by the National Institute of Mental Health (NIMH) failed to find any benefit to antidepressant use for patients with Bipolar I and II depression over the course of 26 weeks [1]. In contrast to the manic phase of the illness, where a fairly large variety of effective treatments are available – most notably antipsychotic and antiepileptic agents – in bipolar depression efficacious therapeutics are scarce. This is especially worrisome because the long-term course of bipolar disorder (BPD) is dominated by recurrent depressive episodes and lingering depressive symptoms rather than hypomanic/manic episodes [2].

This chapter will review the efficacy and safety of several novel therapies for bipolar depression. Promising drug targets and agents for bipolar depression involve several systems, including the melatonin and serotonergic

(5-HT2C receptor) systems, the dopaminergic system, the glutamatergic system, and the hypothalamic-pituitary adrenal (HPA) axis. In addition, the GSK intracellular signaling cascade, the arachidonic acid cascade, and the oxidative stress system appear to be worthy of further study. This chapter will review several specific agents, including modafinil, pramipexole, N-acetyl cysteine (NAC), scopolamine, agomelatine, riluzole, memantine, ketamine, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) potentiators, ketoconazole, mifepristone, celecoxib, creatine, and uridine RG2417. Table 1 summarizes the use and profile of these drugs, all of which meet the category of clinical evidence rating (see Ch. 9) of B, C, or D. The chapter does not review studies in which the treatment of bipolar depression was not the primary issue. Omega-3 fatty acids will also not be reviewed here as they have been extensively reviewed elsewhere (see [3]) and because a large, randomized, controlled study failed to find significant benefits for their use in bipolar depression [4]. Finally, we will not review non-pharmacological somatic treatments (see Ch. 11 for a thorough review of this topic).

Drugs that affect multiple systems

Modafinil

Modafinil is currently approved by the U.S. Food and Drug Administration (FDA) as a wakefulness-promoting agent for the treatment of excessive daytime sleepiness in narcoleptic patients [5]. The presumptive mode of action of this drug is currently unknown, but is hypothesized to be multisystemic in origin. Modafinil has been reported to affect the following neurotransmitter systems: glutamate, GABA, hypocretin, and to a lesser extent, the dopaminergic and noradrenergic systems [6].

Clinically, modafinil appears to benefit patients with mood disorders, particularly in cases where sedation is clinically troublesome. In a 6-week, randomized, double-blind, placebo-controlled evaluation of modafinil (mean daily dose 177 mg) in subjects with bipolar I or II depression who did not adequately respond to mood stabilization with or without adjunctive antidepressant therapy (n = 87), there was both greater baseline to endpoint change and change in week 2 onwards in patients treated with modafinil than with placebo [7]. No manic switches were reported. In another study, Frye and colleagues (unpublished, reported in [8]) compared the add-on modafinil (100 or 200 mg in the morning for 3 weeks) to placebo in the treatment of patients with BPD who also had residual fatigue, depressive symptoms, or both. The study drug was significantly more effective than placebo on a variety of scales, including baseline to endpoint change on the Inventory for Depressive Symptoms (IDS), percentage response rate, remission rate, and Clinical Global Impression (CGI) improvement. In addition, modafinil was not found to be significantly associated with treatment-emergent mania. One published

Table 1. Putative drug targets and agents for the treatment of BPD depression

Drug target	Drug/dose	Population	Study design	Results	Presumptive mechanism	Side effects	Ref
Multiple	Modafinil (mean dose 177 mg/day)	87 BPD I or II	DB, PC, add-on	Greater baseline to endpoint change in modafinil *versus* placebo, and from week 2 on between groups; no manic switches	Largely unknown; reported effects on glutamate, GABA, hypocretin, and to a lesser extent, the dopaminergic and noradrenergic systems	No statistically significant side effects. More common side effects included headache, insomnia	[7]
Dopaminergic and Bcl-2	Pramipexole 1–2.5 mg/day	22 BPD I or II	DB, PC, add-on, 6 weeks	Response: Pramipexole: 67%, PBO: 20%; no difference in manic switch; one patient on pramipexole became hypomanic	D2/3 agonist and Bcl-2 enhancer	Nausea more common with pramipexole; other side effects reported include sedation and headache	[12]
Dopaminergic and Bcl-2	Pramipexole 1–3 mg/day	21 BPD II	DB, PC, add-on, 6 weeks	Response: Pramipexole: 60%, PBO: 9%; no difference in manic switch	D2/3 agonist and Bcl-2 enhancer	No statistically significant difference in side effects between the groups; more common side effects with pramipexole: insomnia, tremor, gastrointestinal complaints, and somnolence	[11]
Oxidative stress (Glutathione)	N-Acetyl cysteine (NAC) (1 g twice daily)	75 BPD	DB, PC, add-on, 24 weeks	NAC significantly improved MADRS scores by endpoint	Enhances brain glutathione levels restoring oxidative imbalances	No statistically significant differences in side effects; more common side effects included headaches (18% NAC, 8% placebo), heartburn(16% NAC, 8% placebo), and increased pain in joints (16% NAC, 8% placebo).	[17]

(Continued on next page)

Table 1. (Continued)

Drug target	Drug/dose	Population	Study design	Results	Presumptive mechanism	Side effects	Ref
Cholinergic	Scopolamine hydrobromide infusion 1–2–4.0 μg/kg	10 UP, 9 BPD	DB, PC	Significant reductions in MADRS scores comparing endpoint with baseline; no manic switches	Antimuscarinic	Side effects numerically more common with scopolamine: dry mouth, blurred vision, lightheadedness, dizziness, and hypotension; euphoria was reported to be no different than placebo	[29]
Melatonin and Seratonergic (5-HT2C)	Agomelatine 25 mg/day	21 BPD I	Open-label, add-on, 6 weeks acute, 46 weeks extension	Response: acute phase: 81%; no significant side effects in acute phase or manic switches	Agonist of melatonin MT1 and MT2 receptors and 5-HT2C antagonist	No significant adverse events during the acute phase; during the extension phase three of 19 experienced hypomanic/manic episodes, one of which was treatment related	[45]
Glutamate release and AMPA receptor	Riluzole 100–200 mg/day	14 BPD	Open-label, 8 weeks, add-on	Significant reductions in MADRS scores comparing endpoint with baseline; no manic switches	Inhibitor of glutamate release, enhancer of AMPA trafficking and expression of glutamate reuptake transporters	Most common side effects were fatigue, decreased salivation, reduced sleep, nausea, weight loss, and blurred vision	[56]
NMDA antagonist (use dependent)	Memantine 10–20 mg/day	2 BPD, 4 weeks and 2nd case not specified	Case series, add-on	Improvement in cognition and mood symptoms	Use dependent NMDA antagonist	Not specified	[61]
Glucocorticoid synthesis	Metyrapone 2,000–4,000 mg/day	3 BPD, 6 UP	Open-label, 2 weeks	5/9 responded. Reduction in MADRS was correlated to decrease in 11-deoxycortisol metabolites	Inhibitor of GC synthesis	Not specified	[70]

(Continued on next page)

Table 1. (Continued)

Drug target	Drug/dose	Population	Study design	Results	Presumptive mechanism	Side effects	Ref
Glucocorticoid synthesis	Ketoconazole 400–800 mg/day	8 UP, 2 BPD, 7 completers	Open-label, 6 weeks	7/7 completers had gradual improvement in mood	Inhibitor of GC synthesis	Three subjects dropped out because of side effects	[71]
Glucocorticoid synthesis	Ketoconazole up to 800 mg/day	6 BPD I or II	Open-label, add-on, 4 weeks	All three completers responded on HAM-D	Inhibitor of GC synthesis	Mild nausea and constipation	[69]
GR II	Mifepristone 600 mg/PBO	20 BPD, add-on	DB PC CO, 1 week	Statistically significant improvement in MADRS and cognition	GR II antagonist	No dropouts due to side effects and no manic switches	[72]
DHEA	DHEA max 90 mg/day	20 UP, 2 BPD	DB PC, 6 weeks monotherapy/ add-on	Response: 5/11 on DHEA and one (0/11) on PBD	DHEA	Well tolerated; no subjects dropped out because of side effects	[86]
Arachidonic acid metabolism	Celecoxib 400 mg/day	28 BPD depressed or mixed episode	DB, PC, add-on, 6 weeks	Celecoxib was more effective than placebo only at week 1 but not at study endpoint	COX-2 inhibitor	Well tolerated; two patients dropped out because of rash	[81]
Bioenergetics	Creatine 3–5 g/day	8 UP, 2 BPD	Open-label, add-on, 4 weeks	Significant improvement in depressive symptoms for MDD patients. Both BPD patients developed hypomania/mania	Brain energy homeostasis	Mild adverse events; two complained of transient nausea and one of constipation. Both BPD patients developed hypomania/mania	[83]
Bioenergetics	Uridine RG2417; dose unknown	84 BPD, 6 weeks	DB, PC, monotherapy	Significant improvement in MADRS scores compared to placebo	Nucleoside uridine	Not specified	*

Abbreviations: BPD: bipolar disorder, CO: crossover, DB: double blind, DHEA: dehydroepiandrosterone, GC: glucocorticoid, GR: glucocorticoid receptor, HAM-D: Hamilton Depression Rating Scale, MADRS: Montgomery-Asberg depression rating scale, PBO: placebo, PC: placebo controlled, UP: unipolar depression.

* http://www.medicalnewstoday.com/articles/88213.php

case report described a manic switch in a patient with treatment-resistant bipolar depression who was treated with modafinil [9], and two cases of modafinil-induced irritability and aggression in two BPD patients have also been described [10].

The dopaminergic system and Bcl-2

Pramipexole

Pramipexole, a synthetic aminothiazole derivative, is a dopamine D2/D3 receptor agonist that is currently approved by the FDA for the treatment of Parkinson's disease. An abundance of data indicate that it has D3 preferring effects (see [11]). Two small, randomized, placebo-controlled trials have examined the effectiveness of pramipexole in the treatment of bipolar depression. Goldberg and colleagues randomized 22 patients with bipolar depression to receive either pramipexole (1.0 to 2.5 mg/day) plus a mood stabilizer, or placebo plus a mood stabilizer [12]. Pramipexole was well-tolerated, and more patients in the pramipexole group achieved a ≥50% reduction from their baseline Hamilton Depression Rating Scale (HAM-D) scores as well as a greater mean change in their HAM-D scores over the 6-week study duration. Additionally, the switch rates into mania and hypomania were not higher than in the placebo group. Side effects were mild.

Zarate and colleagues randomized 21 BPD II patients to receive either pramipexole (1.0–3.0 mg/day) plus a mood stabilizer, or placebo plus a mood stabilizer [11]. They found that 60% of the participants in the pramipexole group had a therapeutic response (as defined by a 50% reduction in Montgomery-Asberg Depression Rating Scale (MADRS) scores) compared to 9% in the placebo group. Pramipexole appeared to be well-tolerated. These encouraging results need confirmation by a Category A study.

Notably, pramipexole upregulates the anti-apototic protein Bcl-2 in several brain areas [13, 14]; it is quite possible that lithium's antidepressant potentiating effects may be due to its ability to similarly and robustly upregulate Bcl-2 [14], which has traditionally been viewed as a 'long-term neuroprotective protein'. Future studies would have to investigate whether selective Bcl-2 enhancers without dopaminergic effects also have antidepressant effects in bipolar depression.

Oxidative stress

N-acetyl cysteine (NAC)

There is increasing evidence that mood disorders are associated with oxidative stress. Glutathione is the main antioxidant substrate in all tissue, and its pro-

duction is rate-limited by its precursor, cysteine; notably, glutathione alterations have been reported in BPD [15, 16]. NAC would thus increase glutathione levels, leading to postulated benefits in BPD because of its antioxidant properties. A recent study by Berk and colleagues reported that NAC was indeed effective in the treatment of BPD [17], and the authors hypothesized that NAC's efficacy might be due to its effects on oxidative stress. In this randomized, double-blind, multicenter, placebo-controlled study, 75 patients with BPD were treated with NAC (1 g twice daily) during the maintenance phase; NAC was added on to treatment as usual over 24 months followed by a 4-week washout phase. The investigators found that NAC significantly improved MADRS and most secondary scale scores by endpoint. Improvement was seen in the Global Assessment of Functioning (GAF) Scale and the Social and Occupational Functioning Assessment Scale (SOFAS) at 8 weeks, and the MADRS at 20 weeks. The benefits obtained were lost shortly after discontinuing the study medication. There were no significant differences in side effects compared to placebo; side effects numerically greater than placebo were headaches (18% NAC, 8% placebo), heartburn (16% NAC, 8% placebo), and increased joint pain (16% NAC, 8% placebo).

The cholinergic system

Scopolamine

Over three decades ago, Janowsky introduced the 'cholinergic-adrenergic imbalance hypothesis' of BPD [18]. He postulated that an imbalance of the regulatory processes of the cholinergic-adrenergic interface might be linked to the pathophysiology of mood disorders, and indeed there is a lengthy history of anticholinergic drug studies in mood disorders research. On a genetic level, there is still little evidence that a dysregulation of the cholinergic system is involved in BPD. One study found an association between 19 cholinergic genes and BPD [19]. In animal models, it has been reported that rats bred for an increased sensitivity of muscarinic receptors showed a behavioral phenotype similar to patients with depression; these animals presented with lethargy, lack of pleasure, and behavioral despair [20]. In humans, cholinergic hyperactivity results in a worsening of depressive symptoms in patients with major depressive disorder (MDD) [18]. Experiments add further support to this theory, as neuroendocrine and pupillary responses to cholinergic activity were found to be supersensitive in depressed subjects [21] and attenuated in manic subjects [22]; improvement of manic symptoms with lithium and valproate leads to normalization of pupillary responses [22].

Cannon and colleagues performed a positron emission tomography (PET) imaging study in patients with BPD and found reduced muscarinic type 2 receptor binding in the anterior cingulate cortex [23]. Additional evidence for an imbalance of the cholinergic system in BPD comes from small controlled

trials with physostigmine (a short-acting cholinesterase inhibitor), which found a rapid but only transitory reduction in manic symptoms following single or multiple intravenous injections [24, 25]. Additional studies with the cholinesterase inhibitor donepezil obtained mixed results in mania [26, 27].

As mentioned above, there is a lengthy history of anticholinergic drug studies in mood disorder research. Initially, the tricyclic antidepressants were believed to be largely effective due to their anticholinergic properties. Early studies found that the anticholinergic drug biperiden had antidepressant properties in 10 severely depressed inpatients [28]. However, this neurotransmitter system remained largely untapped for several decades, perhaps because anticholinergic side effects were a fairly common complaint and reason for discontinuing tricyclic antidepressants in depressed patients. More recently, Furey and Drevets (2006) found that the antimuscarinic drug scopolamine had significant antidepressant effects in subjects with either unipolar or bipolar depression; these effects were reportedly of rapid onset (usually within 1 week) [29]. In the first of two studies, four testing sessions were performed in random order under double-blind conditions, during which subjects received a 15-min intravenous infusion of a saline placebo followed by three doses of scopolamine hydrobromide (2.0, 3.0, and 4.0 μg/kg). In the second study, subjects received a 15-min intravenous infusion of a placebo saline solution or a single dose of scopolamine hydrobromide, 4.0 μg/kg. Patients receiving scopolamine had no significant increase in manic symptoms, and only one patient developed euphoria suggesting that the benefits of scopolamine were not simply due to euphoria. Despite these promising results, the potential side effect of inducing cognitive deficits will need to be addressed when developing scopolamine or similar agents for use in the treatment of BPD.

The melatonin and serotonergic (5-HT2C) systems

Agomelatine

The pineal hormone melatonin produces most of its biological effects via G protein-coupled melatonin receptors (MT1 and MT2) that are mostly expressed in brain. Some studies have reported that patients with BPD, the non-affected offspring of probands with BPD, and monozygotic twins discordant for BPD have an enhanced sensitivity of the melatonin suppressing effects of light [30–32]. However, other investigators did not finding melatonin suppression by light in euthymic BPD patients [33]. Initial reports of a significant association between the Δ502–505 polymorphism in GPR50 (also known as H9, melatonin-related receptor or ML1X, located on Xq28) and susceptibility to BPD [34] have not been replicated [35]. The mood stabilizers lithium and valproate were found to reduce melatonin light sensitivity in healthy volunteers [36, 37]. However, case reports and series indicate mixed results with

melatonin in patients with BPD [38, 39]. No controlled studies of melatonin have been published in BPD.

Agomelatine is a potent agonist of melatonin MT1 and MT2 receptors, and 5-HT2C antagonists have been reported to have antidepressant properties. *In vivo* studies indicate that agomelatine increases both norepinephrine and dopamine in frontal cortex. Chronic agomelatine treatment also increases cell proliferation and neurogenesis in the ventral dentate gyrus, as well as increased survival of these newly formed cells [40]. Agomelatine has antidepressant-like properties in animal models [41, 42] and in anxiety (as assessed by the social interaction test and the Vogel conflict test) [43]; notably, anxiety symptoms commonly co-occur in patients with mood disorders and have significant negative prognostic implications.

Several large, multicenter, multinational, placebo-controlled, short-term studies in MDD have found that agomelatine is a clinically effective and well-tolerated antidepressant [44]. With regards to bipolar depression, 21 patients with BPD I who were experiencing a major depressive episode and had a HAM-D score of ≥18 were treated openly with agomelatine. All patients received 25 mg/day of agomelatine for 6 weeks with a possible extension of up to 46 weeks in combination with either lithium (n = 14) or valpromide (n = 7). Using intent-to-treat data, 81% of patients met criteria for marked improvement at study endpoint, and 47% responded as early as the first week of treatment. Afterwards, 19 patients entered the 1-year extension phase of the study, and, 11 completed it. There were no dropouts due to adverse events during the acute phase of treatment (6 weeks), although six patients experienced serious adverse events during the 1-year period. Three lithium-treated patients experienced manic or hypomanic episodes during the optional extension period, one of which was treatment-related [45].

The glutamatergic system

Contemporary theories of the etiopathogenesis of BPD and recurrent MDD posit that they result from alterations in cellular resilience and neuroplasticity, and the glutamatergic system is being recognized as a likely contributor to the impairments in brain neuroplasticity and cellular resilience observed in patients with BPD. The preclinical evidence supporting the role of the glutamate in the pathophysiology of depression or mechanism of action has been summarized elsewhere [46]. Glutamate is the major excitatory synaptic neurotransmitter in the brain. Its crucial functions include mediating neurotransmission across excitatory synapses, and modulating various physiological functions in the mammalian central nervous system (CNS) such as synaptic plasticity, learning, and memory [47–50]. Excessive concentrations of glutamate are hypothesized to be involved in the etiopathophysiology of several neurodegenerative illnesses. Consequently, several drugs have been created in an attempt to modulate these abnormal concentrations. Evidence that these com-

pounds are neuroprotective in humans with ischemic/traumatic or neurodegenerative disease is still pending.

Several of the glutamatergic compounds being studied as neuroprotective agents have either been or are now undergoing testing in 'proof-of-concept' studies in patients with severe mood disorders [14]. The glutamatergic modulators that are being developed target either the glutamate receptors (N-methyl-D-aspartate (NMDA), AMPA, metabotropic) directly or glutamate before it is released into the extracellular space.

Emerging data indicate that glutamate has an important role in both acute and long-term processes involved in the mode of action of antidepressants and/or mood stabilizers. Synaptic potentiation (i.e., AMPA trafficking) by enhancing AMPA throughput is thought to be involved in acute antidepressant response, while the positive neurotrophic changes resulting from glutamatergic modulators are perhaps more relevant to reducing the recurrence of mood episodes and minimizing the deleterious effects of chronic aberrant neurobiology.

Riluzole

Riluzole is a blood-brain-penetrant glutamatergic modulator with neuroprotective and anticonvulsant properties, and the only drug approved by the FDA for the treatment of the degenerative motor-neuron disease amyotrophic lateral sclerosis (ALS). It acts on the glutamatergic system in diverse ways, including inhibiting glutamate release, enhancing AMPA trafficking by increasing membrane insertion of AMPA subunits GluR1 and GluR2 [51], and enhancing the activity of glutamate reuptake transporters (GLAST, GLT1, and EAAC1) [52]. Riluzole is also known to stimulate the synthesis of growth factors, including brain derived neurotrophic factor (BDNF) in cultured mouse astrocytes [53]; BDNF is implicated in the mechanism of antidepressant action and was recently shown to have antidepressant-like properties in animal models (Gerard Sanacora, personal communication).

Several clinical studies have found that riluzole has antidepressant effects in patients with unipolar depression [54, 55]. Overall, riluzole was well-tolerated in these trials. In bipolar depression, riluzole was studied in combination with lithium [56]. In this study, significant reductions in MADRS scores comparing endpoint with baseline were found for 14 bipolar depressed patients who received riluzole (100–200 mg per day for 6 weeks). These preliminary results need to be confirmed in controlled studies. In mice, pretreatment with riluzole 10 mg/kg, but not 3 mg/kg, moderately decreased amphetamine-induced, but not MK-801-induced, hyperlocomotion [57]. This characteristic suggests that riluzole might have 'antimanic-like' properties, although additional studies are needed to confirm this.

Memantine

Memantine is approved for the treatment of Alzheimer's disease. Its principal mechanism of action lies in the fact that it is a noncompetitive NMDA antagonist in a 'use dependent' manner (it enters and blocks the channel only when there is an excess of extracellular glutamate concentrations). At doses of 5–20 mg/day, it is a fairly selective NMDA receptor antagonist with negligible affinity for other receptors that have been implicated in antidepressant action.

Memantine has antidepressant-like effects [58, 59] in animal studies; in human studies however, a double-blind, placebo-controlled trial of individuals with MDD found that memantine had no antidepressant effects [60]. There is only one report of memantine use in bipolar depression. In this case series involving two patients, memantine at doses of 10–20 mg/day improved depressive symptoms and cognitive performance in patients with BPD when added to ongoing mood stabilizer therapy [61]. Further studies are necessary to address its potential role in bipolar depression.

Ketamine

Contrary to the evidence presented above suggesting that memantine does not possess antidepressant effects in patients with MDD, there is increasing proof that the higher affinity NMDA receptor antagonist, ketamine, has antidepressant effects. Two controlled studies found that ketamine resulted in rapid antidepressant effects in patients with treatment-resistant MDD [62, 63]. The effects noted in the study by Zarate and colleagues were rapid (within 2 h), robust, and relatively sustained (lasting approximately 1 week). Because of the inherent propensity of the compound to produce cognitive deficits and psychotomimetic effects, its use at this time remains limited to the research setting. Studies with more selective subtype NMDA antagonists are underway, in order to determine whether these have antidepressant effects that can occur safely without causing ketamine's undesirable side effects. Emerging data suggest that ketamine's antidepressant properties occur in part by enhancing AMPA throughput [64]. Although no studies of ketamine's effects in bipolar depression have been conducted, the results obtained in patients with treatment-resistant MDD are worth mentioning here. A trial evaluating the use of ketamine in bipolar depression is currently underway at the NIMH.

AMPA potentiators

AMPA receptors are ionotropic receptors that play a major role in learning and memory. These types of glutamatergic receptors mediate the fast component of excitatory neurotransmission. Numerous classes of compounds modulate

AMPA receptors by binding to their allosteric sites and are termed AMPA receptor positive modulators or AMPA Receptor Potentiators (ARPs). ARPs regulate AMPA receptors indirectly by slowing the receptor desensitization rate and/or deactivation in the presence of an agonist (e.g., AMPA and glutamate (see [65] for a review)). These compounds are under active investigation as treatments for cognition, depression, anxiety, stroke, and Parkinson's disease [66]. Chronic treatment with traditional antidepressants increases the expression of AMPA receptors in hippocampal membranes and the phosphorylation of AMPA receptor subunits [46].

The effects of standard treatments for BPD (i.e., lithium, valproate, and lamotrigine) on AMPA receptors suggest that those agents with a predominantly antidepressant profile – namely lamotrigine and riluzole – significantly enhance the surface expression of GluR1 and GluR2 in a time- and dose-dependent manner in cultured hippocampal neurons [51]. In contrast, the predominantly antimanic agents lithium and valproate significantly reduce surface expression of GluR1 and GluR2 [67]. These findings imply that regulation of GluR1/2 surface levels and function may be involved in the different clinical profile of anticonvulsants, and suggests that drugs that mimic these biochemical effects might have a similar therapeutic role.

The glucocorticoid system

Dysfunction of the hypothalamic-pituitary adrenal (HPA) axis has been well-described in bipolar depression. For instance, hypercortisolemia may be central to the etiopathogenesis of both depressive symptoms and the neurocognitive deficits observed in BPD. Attempts to better normalize the effects of cortisol, which may potentially restore HPA axis integrity, have been the focus of recent research. The antiglucocorticoid agents studied in the treatment of mood disorders include cortisol synthesis inhibitors (aminoglutethimide, ketoconazole, and metyrapone) and corticosteroid receptor antagonists (mifepristone and ketoconazole), as well as hydrocortisone, dexamethasone, and dehydroepiandrosterone (DHEA) (reviewed in [68]). Only a few of these compounds have been tested in bipolar depression [69–72]. With regards to the glucocorticoid synthesis inhibitors, fewer than 20 patients with bipolar depression have received this class of drugs; the largest study was an open-label add-on, 4-week study of ketoconazole (up to 800 mg/day) in six patients [69]. Three patients who received a dose of at least 400 mg/day had substantial reductions in depressive symptoms and no development of manic symptoms; cortisol levels were not lowered in any of the subjects. The significant toxicity risk and drug interactions associated with ketoconazole preclude its use on a chronic basis for mood disorders.

Only one placebo-controlled study of an antiglucocorticoid for bipolar depression has been performed [72]. Mifepristone (RU-486) is a non-selective antagonist of the glucocorticoid receptor that has been reported to have anti-

depressant and antipsychotic properties in patients with psychotic depression (reviewed in [68]). Although a recent letter to the editor indicates that two large Phase III studies failed to find significant antipsychotic or antidepressant effects for mifepristone [73], a controlled study suggests that it may possess antidepressant and cognitive enhancing properties in bipolar depression. In this double-blind, placebo-controlled, crossover study, Young and colleagues (2004) compared mifepristone (600 mg) to placebo in 20 subjects with bipolar depression and found that, over the course of the 6-week study, neurocognitive and mood symptoms improved [72]. If mifepristone is found to have beneficial effects in bipolar depression, its use will most likely be limited to acute depressive episodes; longer treatment could result in significant complications including adrenal insufficiency and hepatic injury [74]. A large controlled study with mifepristone in bipolar depression is currently underway (NCT0035912 by Alan Young at the University of British Columbia).

Glycogen synthase kinase-3 (GSK-3)

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase constitutively active in cells, and is deactivated by signals originating from numerous signaling pathways (e.g., the Wnt pathway, the PI-3' kinase (PI3K) pathway, protein kinase A (PKA), and protein kinase C (PKC)) [75]. Preclinical evidence implicates GSK-3 in either the direct or downstream mechanism of action of many other mood stabilizers and antidepressants currently in use (see [76]). In addition, GSK-3 modulates apoptosis and synaptic plasticity and may also modulate the circadian cycle by modulating gene expression of proteins involved in these processes. Recent animal behavioral data (from pharmacologic and genetic models) have shown that manipulation of the GSK-3 signaling cascade produces both antimanic and antidepressant effects in animal models of depression and mania [76–78]. In attempting to achieve selectivity for GSK-3 inhibition, it is critical to avoid the side effects that may occur with GSK inhibitors, which have been putatively linked with cardiac hypertrophy and cancer (due to upregulation of the Wnt pathway, which is common in human cancers) [76].

No GSK inhibitors are included in Table 1 because none are currently available for clinical use.

Arachidonic acid metabolism

Celecoxib

There is increasing evidence for the involvement of the arachidonic signaling pathway in BPD. Administration of the nonselective COX inhibitors indomethacin and piroxicam in rats prevented amphetamine-stimulated loco-

motor activity, and blocked cocaine sensitization (both are rodent models of mania). Moreover, inhibition of COX-2 with NS-398 attenuated restraint stress-induced oxidative changes (a model of depression). In olfactory bulbectomized rats, the COX-2 inhibitor celecoxib showed antidepressant-like properties [79]. In a 6-week, double-blind, placebo-controlled trial in humans, celecoxib showed some antidepressant properties. Muller and colleagues (2006) found that celecoxib (400 mg/day), when added to reboxetine in patients with MDD, produced significant antidepressant effects compared to placebo [80]. Recently, a 6-week, double-blind, placebo-controlled trial found that celecoxib (400 mg/day) was effective in patients with Bipolar I or II depression when added to ongoing mood stabilizer treatment; however, add-on celecoxib was more effective than placebo only at week 1, not at study endpoint [81].

Notably, the extent of celecoxib's ability to penetrate the blood brain barrier remains unclear. In addition, it is also presently unclear whether directly targeting COX-2 is worthwhile, because selective COX-2 inhibitors may be associated with an increased risk of adverse cardiovascular outcomes [82].

Bioenergetics

Creatine

Creatine plays an important role in brain energy homeostasis and altered brain energy metabolism, and has been implicated in BPD. An open-label study consisting of 10 treatment-resistant depressed patients (two of whom had BPD) found that 3–5 mg/day of creatine monohydrate added to ongoing treatment led to a significant improvement in depressive symptoms in patients with MDD [83]. However, the two patients with BPD developed transient hypomanic/manic symptoms. Further studies are warranted to clarify the role of creatine in BPD.

Uridine RG2417

Uridine RG2417 (Repligen corporation) – a biological compound essential for the synthesis of DNA and RNA – is currently in development for the treatment of neuropsychiatric disorders and neurodegenerative diseases. An earlier study suggested that RG2133, the prodrug of RG2417, had antidepressant-like effects in an animal model. RG2417 was recently found to be effective in a Phase IIa multi-site study of bipolar depression. In this multicenter study, 84 patients received either RG2417 or a placebo twice a day (unpublished findings). Over the 6-week treatment period, patients receiving RG2417 experienced a statistically significant improvement in depressive symptoms compared to those patients receiving placebo as assessed by the MADRS ($p = 0.03$), and a strong trend towards improvement on the CGI-BP-C

($p = 0.06$). This study was conducted under a development agreement with the Stanley Medical Research Institute (study ID # NCT00322764; study details are available at: http://www.medicalnewstoday.com/articles/88213.php).

Conclusion

As this chapter has described, a number of targets/compounds could result in putative treatments for bipolar depression. These include the melatonin and serotonergic (5-HT2C receptor) systems, the dopaminergic system, the glutamatergic system, and the HPA axis. In addition, the GSK intracellular signaling cascade, the arachidonic acid cascade, and the oxidative stress system all merit further study. As detailed above, a number of drugs not in routine clinical use are being used and studied in the treatment of bipolar depression. These treatments are currently available (with the exception of uridine RG2417) but are not anticonvulsants, antipsychotics, or conventional antidepressants. The drugs reviewed here include modafinil, pramipexole, N-acetyl cysteine, scopolamine, agomelatine, riluzole, memantine, ketamine, AMPA potentiators, ketoconazole, mifepristone, celecoxib, creatine, and uridine RG2417. It is important to emphasize that none of these drugs are FDA-approved for the treatment of MDD or bipolar depression. In addition, most of the evidence presented here comes from case reports, case series, or proof-of-concept studies, some with very small sample sizes. Thus, generalizability of such preliminary findings to current clinical practice patterns would be premature. We believe, however, that it is of considerable interest to understand where drug development for BPD may be heading. Some other examples of candidate drugs for BPD in early development are reviewed elsewhere [84].

A better understanding of the neurobiological underpinnings of BPD, informed by preclinical and clinical research, will be essential for the future development of targeted therapies that are more effective, act more rapidly, and are better tolerated than currently available treatments. Of the pharmacological agents reviewed here, modafinil, pramipexole, NAC, scopolamine, and mifepristone have been tested and found to have antidepressant properties in controlled studies. Larger controlled studies should be considered for these compounds. This chapter does not review some important drug targets for BPD – for instance, PKC – because this target has been implicated more in the treatment of bipolar mania than bipolar depression. The reader is referred elsewhere for more information on PKC [85].

Finally, future drug development will also need to focus on identifying molecular targets. Following this path for drug development will result in a better understanding of the cellular and molecular underpinnings of severe mood disorders, and the manner in which they are associated with regional impairments of structural plasticity and cellular resiliency [14]. Ultimately, such ‘plasticity enhancing’ strategies may prove to be very useful in the treatment of mood disorders.

Acknowledgements
We would like to acknowledge the support of the Intramural Research Program of the National Institute of Mental Heath, the Stanley Medical Research Institute and NARSAD. Drs Zarate and Manji are listed among the inventors on a patent application submitted for the use of ketamine in depression. They have assigned their rights on the patent to the US government.

References

1 Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ et al (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 356: 1711–1722
2 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59: 530–537
3 Montgomery P, Richardson AJ (2008) Omega-3 fatty acids for bi-polar disorder. *Cochrane Database Syst Rev* 16: CDD005169
4 Keck PE Jr, Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, Altshuler LL, Kupka R, Nolen WA, Leverich GS et al (2006) Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry* 60: 1020–1022
5 Littner M, Johnson SF, McCall VW, Anderson WM, Davila D, Hartse SK, Kushida CA, Wise MS, Hirshkowitz M, Woodson BT et al (2001) Practice parameters for the treatment of narcolepsy: an update for 2000. *Sleep* 24: 451–466
6 Ballon JS, Feifel D (2006) A systematic review of modafinil: Potential clinical uses and mechanisms of action. *J Clin Psychiatry* 67: 554–566
7 Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE Jr, Walden J, Leverich GS, Altshuler LL, Nakelsky S, Hwang S et al (2007) A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 164: 1242–1249
8 Post RM, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE Jr, Leverich GS, Kupka R, Nolen WA, Grunze H (2006) New findings from the Bipolar Collaborative Network: clinical implications for therapeutics. *Curr Psychiatry Rep* 8: 489–497
9 Wolf J, Fiedler U, Anghelescu I, Schwertfeger N (2006) Manic switch in a patient with treatment-resistant bipolar depression treated with modafinil. *J Clin Psychiatry* 67: 1817
10 Ranjan S, Chandra PS (2005) Modafinil-induced irritability and aggression? A report of 2 bipolar patients. *J Clin Psychopharmacol* 25: 628–629
11 Zarate CA Jr, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, Charney DS, Manji HK (2004) Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry* 56: 54–60
12 Goldberg JF, Burdick KE, Endick CJ (2004) Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 161: 564–566
13 Takata K, Kitamura Y, Kakimura J, Kohno Y, Taniguchi T (2000) Increase of bcl-2 protein in neuronal dendritic processes of cerebral cortex and hippocampus by the antiparkinsonian drugs, talipexole and pramipexole. *Brain Res* 872: 326–341
14 Zarate CA Jr, Singh J, Manji HK (2006) Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry* 59: 1006–1020
15 Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Cereser KM, Santin A, Gottfried C et al (2007) Serum S100B and antioxidant enzymes in bipolar patients. *J Psychiatr Res* 41: 523–529
16 Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkiline N (2002) Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. *Cell Biochem Funct* 20: 171–175
17 Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI (2008) N-Acetyl Cysteine for depressive symptoms in bipolar disorder-a double-blind randomized placebo-controlled trial. *Biol Psychiatry* 64: 468–475
18 Janowsky DS, el-Yousef MK, Davis JM, Sekerke HJ (1972) A cholinergic-adrenergic hypothesis

of mania and depression. *Lancet* 2: 632–635
19 Shi J, Hattori E, Zou H, Badner JA, Christian SL, Gershon ES, Liu C (2007) No evidence for association between 19 cholinergic genes and bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* 144: 715–723
20 Overstreet DH (1993) The Flinders sensitive line rats: a genetic animal model of depression. *Neurosci Biobehav Rev* 17: 51–68
21 Dilsaver SC (1986) Pathophysiology of "cholinoceptor supersensitivity" in affective disorders. *Biol Psychiatry* 21: 813–829
22 Sokolski KN, DeMet EM (2000) Cholinergic sensitivity predicts severity of mania. *Psychiatry Res* 95: 195–200
23 Cannon DM, Carson RE, Nugent AC, Eckelman WC, Kiesewetter DO, Williams J, Rollis D, Drevets M, Gandhi S, Solorio G et al (2006) Reduced muscarinic type 2 receptor binding in subjects with bipolar disorder. *Arch Gen Psychiatry* 63: 741–747
24 Davis KL, Berger PA, Hollister LE, Defraites E (1978) Physostigmine in mania. *Arch Gen Psychiatry* 35: 119–122
25 Khouzam HR, Kissmeyer PM (1996) Physostigmine temporarily and dramatically reversing acute mania. *Gen Hosp Psychiatry* 18: 203–204
26 Burt T, Sachs GS, Demopoulos C (1999) Donepezil in treatment-resistant bipolar disorder. *Biol Psychiatry* 45: 959–964
27 Eden Evins A, Demopulos C, Nierenberg A, Culhane MA, Eisner L, Sachs GS (2006) A double-blind, placebo-controlled trial of adjunctive donepezil in treatment-resistant mania. *Bipolar Disord* 8: 75–80
28 Kasper S, Moises HW, Beckmann H (1981) The anticholinergic biperiden in depressive disorders. *Pharmacopsychiatria* 14: 195–198
29 Furey ML, Drevets WC (2006) Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 63: 1121–1129
30 Hallam KT, Olver JS, Norman TR (2005) Melatonin sensitivity to light in monozygotic twins discordant for bipolar I disorder. *Aust N Z J Psychiatry* 39: 947
31 Lewy AJ, Nurnberger JI Jr, Wehr TA, Pack D, Becker LE, Powell RL, Newsome DA (1985) Supersensitivity to light: possible trait marker for manic-depressive illness. *Am J Psychiatry* 142: 725–727
32 Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Rosenthal NE (1981) Manic-depressive patients may be supersensitive to light. *Lancet* 8216: 383–384
33 Nurnberger JI Jr, Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy AJ, Miller A, Bowman ES, Miller MJ, Rau L et al (2000) Melatonin suppression by light in euthymic bipolar and unipolar patients. *Arch Gen Psychiatry* 57: 572–579
34 Thomson PA, Wray NR, Thomson AM, Dunbar DR, Grassie MA, Condie A, Walker MT, Smith DJ, Pulford DJ, Muir W et al (2005) Sex-specific association between bipolar affective disorder in women and GPR50, an X-linked orphan G protein-coupled receptor. *Mol Psychiatry* 10: 470–478
35 Alaerts M, Venken T, Lenaerts AS, De Zutter S, Norrback KF, Adolfsson R, Del-Favero J (2006) Lack of association of an insertion/deletion polymorphism in the G protein-coupled receptor 50 with bipolar disorder in a Northern Swedish population. *Psychiatr Genet* 16: 235–236
36 Hallam KT, Olver JS, Horgan JE, McGrath C, Norman TR (2005) Low doses of lithium carbonate reduce melatonin light sensitivity in healthy volunteers. *Int J Neuropsychopharmacol* 8: 255–259
37 Hallam KT, Olver JS, Norman TR (2005) Effect of sodium valproate on nocturnal melatonin sensitivity to light in healthy volunteers. *Neuropsychopharmacology* 30: 1400–1404
38 Bersani G, Garavani A (2000) Melatonin add-on in manic patients with treatment resistant insomnia. *Biol Psychiatry* 24: 185–191
39 Leibenluft E, Feldman-Naim S, Turner EH, Wehr TA, Rosenthal NE (1997) Effects of exogenous melatonin administration and withdrawal in five patients with rapid-cycling bipolar disorder. *J Clin Psychiatry* 58: 383–388
40 Banasr M, Soumier A, Hery M, Mocaer E, Daszuta A (2006) Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. *Biol Psychiatry* 59: 1087–1096
41 Bertaina-Anglade V, laRochelle CD, Boyer PA, Mocaer E (2006) Antidepressant-like effects of agomelatine (S 20098) in the learned helplessness model. *Behav Pharmacol* 17: 703–713
42 Papp M, Gruca P, Boyer PA, Mocaer E (2003) Effect of agomelatine in the chronic mild stress

model of depression in the rat. *Neuropsychopharmacology* 28: 694–703
43 Millan MJ, Brocco M, Gobert A, Dekeyne A (2005) Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: role of 5-HT2C receptor blockade. *Psychopharmacology (Berl)* 177: 448–458
44 Montgomery SA, Kasper S (2007) Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. *Int Clin Psychopharmacol* 22: 283–291
45 Calabrese JR, Guelfi JD, Perdrizet-Chevalier C (2007) Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. *Bipolar Disord* 9: 628–635
46 Sanacora G, Zarate CA Jr, Krystal JH, Manji HK (2008) Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov* 7: 426–437
47 Bannerman DM, Good MA, Butcher SP, Ramsay M, Morris RG (1995) Distinct components of spatial learning revealed by prior training and NMDA receptor blockade. *Nature* 378: 182–186
48 Collingridge GL (1994) Long-term potentiation. A question of reliability. *Nature* 371: 652–653
49 Collingridge GL, Bliss TV (1995) Memories of NMDA receptors and LTP. *Trends Neurosci* 18: 54–56
50 Watkins J, Collingridge G (1994) Phenylglycine derivatives as antagonists of metabotropic glutamate receptors. *Trends Pharmacol Sci* 15: 333–342
51 Du J, Suzuki K, Wei Y, Wang Y, Blumenthal R, Chen Z, Falke C, Zarate CA Jr, Manji HK (2007) The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorders. *Neuropsychopharmacology* 32: 793–802
52 Fumagalli E, Funicello M, Rauen T, Gobbi M, Mennini T (2008) Riluzole enhances the activity of glutamate transporters GLAST, GLT1 and EAAC1. *Eur J Pharmacol* 578: 171–176
53 Mizuta I, Ohta M, Ohta K, Nishimura M, Mizuta E, Kuno S (2001) Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes. *Neurosci Lett* 310: 117–120
54 Sanacora G, Kendell SF, Levin Y, Simen AA, Fenton LR, Coric V, Krystal JH (2007) Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry* 61: 822–825
55 Zarate CA Jr, Payne JL, Quiroz JA, Sporn J, Denicoff KD, Luckenbaugh DA, Chandra PS, Charney DS, Manji HK (2004) An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 161: 171–174
56 Zarate CA Jr, Quiroz JA, Singh J, Denicoff KD, De Jesus G, Luckenbaugh DA, Charney DS, Manji HK (2005) An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry* 57: 430–432
57 Lourenco Da Silva A, Hoffmann A, Dietrich MO, Dall'Igna OP, Souza DO, Lara DR (2003) Effect of riluzole on MK-801 and amphetamine-induced hyperlocomotion. *Neuropsychobiology* 48: 27–30
58 Moryl E, Danysz W, Quack G (1993) Potential antidepressive properties of amantadine, memantine and bifemelane. *Pharmacol Toxicol* 72: 394–397
59 Rogoz Z, Skuza G, Maj J, Danysz W (2002) Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. *Neuropharmacology* 42: 1024–1030
60 Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KD, Luckenbaugh DA, Manji HK, Charney DS (2006) A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am J Psychiatry* 163: 153–155
61 Teng CT, Demetrio FN (2006) Memantine may acutely improve cognition and have a mood stabilizing effect in treatment-resistant bipolar disorder. *Rev Bras Psiquiatr* 28: 252–254
62 Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47: 351–354
63 Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63: 856–864
64 Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, Chen G, Manji HK (2008) Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry* 63: 349–352
65 Black MD (2005) Therapeutic potential of positive AMPA modulators and their relationship to AMPA receptor subunits. A review of preclinical data. *Psychopharmacology (Berl)* 179: 154–163
66 Du J, Quiroz JA, Yuan P, Zarate CA Jr, Manji HK (2004) Bipolar disorder: involvement of sig-

naling cascades and AMPA receptor trafficking at synapses. *Neuron Glia Biol* 1: 231–243
67 Du J, Gray NA, Falke C, Chen W, Yuan P, Szabo ST, Einat H, Manji HK (2004) Modulation of synaptic plasticity by antimanic agents: the role of AMPA glutamate receptor subunit 1 synaptic expression. *J Neurosci* 24: 6578–6589
68 Quiroz JA, Singh J, Gould TD, Denicoff KD, Zarate CA Jr, Manji HK (2004) Emerging experimental therapeutics for bipolar disorder: clues from the molecular pathophysiology. *Mol Psychiatry* 9: 756–776
69 Brown ES, Bobadilla L, Rush AJ (2001) Ketoconazole in bipolar patients with depressive symptoms: a case series and literature review. *Bipolar Disord* 3: 23–29
70 Raven PW, O'Dwyer AM, Taylor NF, Checkley SA (1996) The relationship between the effects of metyrapone treatment on depressed mood and urinary steroid profiles. *Psychoneuroendocrinology* 21: 277–286
71 Wolkowitz OM, Reus VI, Manfredi F, Ingbar J, Brizendine L, Weingartner H (1993) Ketoconazole administration in hypercortisolemic depression. *Am J Psychiatry* 150: 810–812
72 Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN (2004) Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology* 29: 1538–1545
73 Carroll BJ, Rubin RT (2008) Mifepristone in psychotic depression? *Biol Psychiatry* 63: E1
74 Rothschild AJ (2003) Challenges in the treatment of depression with psychotic features. *Biol Psychiatry* 53: 680–690
75 Gould TD, Manji HK (2004) The molecular medicine revolution and psychiatry: bridging the gap between basic neuroscience research and clinical psychiatry. *J Clin Psychiatry* 65: 598–604
76 Gould TD, Manji HK (2005) Glycogen synthase kinase-3: a putative molecular target for lithium mimetic drugs. *Neuropsychopharmacology* 30: 1223–1237
77 Gould TD, Einat H, Bhat R, Manji HK (2004) AR-A014418, a selective GSK-3 inhibitor, produces antidepressant-like effects in the forced swim test. *Int J Neuropsychopharmacol* 7: 387–390
78 Gould TD, Zarate CA Jr, Manji HK (2004) Glycogen synthase kinase-3: a target for novel bipolar disorder treatments. *J Clin Psychiatry* 65: 10–21
79 Myint AM, Steinbusch HW, Goeghegan L, Luchtman D, Kim YK, Leonard BE (2007) Effect of the COX-2 inhibitor celecoxib on behavioural and immune changes in an olfactory bulbectomised rat model of depression. *Neuroimmunomodulation* 14: 65–71
80 Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Muller B, Spellman I, Hetzel G, Maino K, Kleindienst N et al (2006) The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry* 11: 680–684
81 Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, Bowden CL, Soares JC (2008) Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol* 23: 87–94
82 Velentgas P, West W, Cannuscio CC, Watson DJ, Walker AM (2006) Cardiovascular risk of selective cyclooxygenase-2 inhibitors and other non-aspirin non-steroidal anti-inflammatory medications. *Pharmacoepidemiol Drug Saf* 15: 641–652
83 Roitman S, Green T, Osher Y, Karni N, Levine J (2007) Creatine monohydrate in resistant depression: a preliminary study. *Bipolar Disord* 9: 754–758
84 Zarate CA Jr, Manji HK (2008) Bipolar disorder: candidate drug targets. *Mt Sinai J Med* 75: 226–247
85 Zarate CA Jr, Singh J, Carlson PJ, Quiroz JA, Jolkovsky L, Luckenbaugh DA, Manji HK (2007) Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar Disord* 9: 561–570
86 Wolkowitz OM, Reus VI, Keebler A, Nelson N, Friedland M, Brizendine L, Roberts E (1999) Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry* 156: 646–649