

Bipolar Disorder: Candidate Drug Targets

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ABSTRACT

Current pharmacotherapy for bipolar disorder is generally unsatisfactory for a large number of patients. Even with adequate modern bipolar pharmacological therapies, many afflicted individuals continue to have persistent mood episode relapses, residual symptoms, functional impairment, and psychosocial disability. Creating novel therapeutics for bipolar disorder is urgently needed. Promising drug targets and compounds for bipolar disorder worthy of further study include both systems and intracellular pathways and targets. Specifically, the purinergic system, the dynorphin opioid neuropeptide system, the cholinergic system (muscarinic and nicotinic systems), the melatonin and serotonin [5-hydroxytryptamine receptor 2C] system, the glutamatergic system, and the hypothalamic-pituitary adrenal axis have all been implicated. Intracellular pathways and targets worthy of further study include glycogen synthase kinase-3 protein, protein kinase C, and the arachidonic acid cascade. *Mt Sinai J Med* 75:226–247, 2008. © 2008 Mount Sinai School of Medicine

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Bipolar disorder (BPD) is one of the most severe illnesses of the major mental disorders and ranks in the top 10 causes of medical disability. It is very common, having a lifetime prevalence of approximately 4.4% (BPD I, 1.0%, and BP II, 1.1%) in the United States.¹ BPD is a complex illness encompassing varying degrees of fluctuating disturbances of

emotions, behavior, thought, cognition, and hedonic and motoric drive over the course of a person's life span. Such varied clinical syndromes are usually encapsulated into episodes for diagnostic and treatment purposes (manic, mixed, hypomanic, and depressive episodes). As a result, the development of BPD therapies occurs first for the acute phases of the illness (manic, mixed, and depressive episodes) and then for the maintenance phase of treatment, even though controlling relapses is the most important aspect in the treatment of BPD. Pharmacologically, the greatest success has been in the treatment of acute manic episodes. There are now many anti-manic agents available for clinical use, although a sizable proportion of patients fail to respond to or tolerate these treatments.² However, for acute depressive episodes and for maintenance treatment, few treatments have been proven to be effective; this is especially of concern because depressive episodes and symptoms and depressive relapse dominate the longitudinal course of BPD.³

Recent large-scale National Institute of Mental Health–funded studies have explored the effectiveness of our standard treatments for patients with recurrent mood disorders, and the news is of concern. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that less than one-third of patients with major depressive disorder achieved remission with an adequate trial of a standard antidepressant after approximately 10 to 14 weeks of treatment. For BPD depression, the use of adjunctive, standard antidepressant medication, in comparison with the use of mood stabilizers, was not associated with increased efficacy after 26 weeks.^{4–6} Except for lithium, all available Food and Drug Administration (FDA)–approved treatments for BPD fall into the category of anticonvulsant or antipsychotic drugs and were originally developed to treat other conditions.⁷ Until recently, no drug has been developed specifically for the treatment of BPD on the basis of an understanding of the neurobiological basis of the illness or of the mechanism of action of existing effective medications. The lack of novel treatments for BPD is undoubtedly due in part to the

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complexity of studying this illness (eg, the difficulty in recruiting patients, natural course of the disease, placebo effects, and high rates of dropout).

In order to determine what neurotransmitter systems/intracellular pathways might be relevant for developing drugs for BPD, we conducted a Medline and web-based search (1990 to October 2007), looking for examples of compounds or drugs that met 1 or more of the following criteria: (1) antimanic effects in humans or beneficial effects on irritability, hyperactivity, or mood; (2) antidepressant properties in bipolar depression; and (3) antidepressant-like properties in animal models and either "antimanic-like" properties in animal models⁸ or antipsychotic-like properties in either humans or animal models of psychosis (eg, prepulse inhibition). Antipsychotic or anticonvulsant drugs were excluded, except for those with predominant effects on α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors. A review of these agents is not included here because this topic has been discussed extensively elsewhere and because it is likely that useful drugs from these classes of compounds will continue to become available for the treatment of BPD but are likely to be comparable in efficacy to existing medications. Finally, it should be noted that the extrapolation of findings from animal studies to humans in the absence of reliable and valid animal models of BPD must be interpreted with caution.

Here we review the drug targets and compounds for BPD meeting these criteria. Several systems are worthy of further study, including (1) the purinergic system, (2) the dynorphin opioid neuropeptide system, (3) the cholinergic system (muscarinic and nicotinic systems), (4) the melatonin and serotonin [5-hydroxytryptamine receptor 2C (5-HT_{2C})] system, (5) the glutamatergic system, and (6) the hypothalamic-pituitary adrenal (HPA) axis. In addition, several intracellular pathways and targets merit further attention, including (1) glycogen synthase kinase-3 (GSK-3) protein, (2) protein kinase C (PKC), (3) the arachidonic acid (AA) cascade, and (4) other candidates. It is important to note that most of the drugs reviewed here are proof-of-concept studies, some with very small sample sizes. Thus, the generalizability of such preliminary findings to current clinical practice patterns would be premature.

SYSTEMS WORTHY OF FURTHER STUDY IN BPD

Purinergic System

Purines play an essential role in energy metabolism and are regulators of neurotransmission (adenosine triphosphate and adenosine); adenosine is a widespread neuromodulator acting mostly through adenosine 1 and 2A receptors. Uric acid is the ultimate step in the metabolism of the purinergic system. In the 19th century, uric acid "diathesis," a predisposition to the accumulation of urea in the body, was believed to cause rheumatism, cardiac disease, and mental illness.⁹ Because lithium urate was found to dissolve urate stones, it was believed that it could be helpful in the treatment of these conditions. In 1949, Cade¹⁰ injected lithium urate into guinea pigs, noted that it had a calming effect, and reasoned that it would be helpful in calming patients with mania. Anumonye *et al.*¹¹ reported that remission in mania was associated with the increased excretion of uric acid. Subsequently, it was hypothesized that a purinergic dysfunction might be involved in the neurobiology of mania,¹² and genetic data implicate purinergic dysfunction in BPD.^{13,14}

The avoidance of adenosine antagonists such as caffeine has been recommended for patients with BPD because of its potential to cause irritability and disrupt the sleep-wake cycle; the latter is a common reason for manic relapse. A case of secondary mania caused by caffeine has been reported.¹⁵ Adenosine agonists have been reported to have sedative, anticonvulsant, anti-aggressive, and antipsychotic properties in animals.¹⁶ With respect to other purinergic modulators, allopurinol has been used for many years for the treatment of gout; it acts by inhibiting xanthine oxidase, a key step in the production of uric acid.¹⁷ Case reports suggest that allopurinol might be effective in the treatment of mania and hyperuricemia.¹⁸ Recently, 2 large, placebo-controlled trials confirmed that the addition of allopurinol to ongoing antimanic/mood-stabilizer therapies resulted in significant antimanic effects. In the first study,¹⁹ 82 subjects were randomized to either blinded allopurinol (300 mg/day) or placebo added to lithium plus haloperidol for 8 weeks. Post-hoc comparisons showed significant improvement as early as day 7 on the Young Mania Rating Scale (YMRS), and the difference between the 2 groups was also significant at the endpoint (8 weeks). Side effects for the 2 groups were comparable. The second study was a 4-week, double-blind, placebo-controlled study involving 150 subjects with acute bipolar mania. The study compared allopurinol (600 mg/day),

dipyridamole (200 mg/day), and placebo added to lithium.²⁰ Further large controlled studies with more selective modulators of the purinergic system are needed to determine what aspects of the purinergic system are relevant to antimanic effects.

Dynorphin Opioid Neuropeptide System

The dynorphin opioid neuropeptide system is involved in mood, motor, cognitive, and endocrine functions. A number of preclinical studies support the evidence of the opioid system's putative involvement in depression. There are 3 well-defined types of opioid receptors: μ , κ , and δ . All these types of opioid receptors have been implicated to different degrees in major depression. A significant reduction (37%–38%) of the prodynorphin messenger RNA (mRNA) expression levels in the amygdalohippocampal area and in the parvocellular division of the accessory basal area in patients with BPD was found.²¹

Kappa Opioid Receptors Kappa opiate agonists such as U50,488 produce analgesia and diuresis and show antipruritic activity.²² Selective kappa opiate antagonists are being explored for their effects in the treatment of a wide variety of conditions, including cocaine addiction²³ and feeding behavior abnormalities,²⁴ and have been proposed as a treatment for psychosis.²⁵ The activation of kappa opiate receptors has depressogenic effects in both animals²⁶ and humans.²⁷ The blockade of kappa opiate receptors results in antidepressant-like properties in animals.²⁸ Recently, evidence of the antidepressant-like properties of the kappa opioid antagonist MCL-144B in the forced swim test (FST) has been reported.²⁹ Thus, it stands to reason that kappa opiate agonists could have antimanic effects. However, it has long been recognized that centrally acting kappa opiate receptor agonists might have limited usefulness in humans because of the psychotomimetic and dysphoric actions that can occur with their use.^{30,31}

Pentazocine No selective kappa agonists are available for testing in humans. However, the analgesic pentazocine (Talwin) penetrates the blood-brain barrier and is a partial agonist at the kappa opiate receptor. In a recent open-label study involving 10 inpatients in the manic phase of BPD with a YMRS score of ≥ 14 , adjunctive pentazocine significantly improved manic symptoms without inducing depression.³² In this inpatient study, subjects received two 50-mg doses of pentazocine 2 hours apart. Symptoms of mania were reported

to be reduced 1 hour after each dose, $>44\%$ after the first dose and 41% after the second dose, and this was not due to sedation. Overall, the study medication was well tolerated; no subject complained of dysphoria when self-rating mood, and significant adverse events or psychotomimetic effects were not observed. It is important to emphasize that this was a small, uncontrolled study. At this time, pentazocine is not advocated for clinical use because excessive doses could lead to serious intoxication³³ and because there have been reports that it induces symptoms of depression and "gloominess" in healthy volunteers.³⁴ However, it will be interesting to follow up this preliminary study with controlled, proof-of-principle studies using more selective kappa opiate agonists in the treatment of mania in order to determine the relevance of kappa opioid receptors in BPD.

Salvinorin Salvinorin-A is a recreational drug derived from the *Salvia divinorum* plant, a member of the sage family.³⁵ It is a naturally occurring hallucinogen identified to be a highly selective full kappa opioid receptor agonist.²⁵ A recent study²⁶ found that salvinorin-A induced depressive-like behaviors in the FST (increased immobility) and intracranial-stimulation test. In this report, the investigators noted that, at the dose of salvinorin-A that caused depressive-like effects, extracellular concentrations of dopamine, but not serotonin, within the nucleus accumbens were reduced. A greater understanding of the mode of action of salvinorin-A will undoubtedly lead to a better understanding of the kappaergic system in human brain function and to the development of a series of novel compounds for potential therapeutic use in neuropsychiatric conditions.³⁶ It should also be noted that the potential for abuse and/or withdrawal of these types of compounds will need to be further studied before they can be of clinical utility.

Cholinergic System

The cholinergic system has long been studied as an important aspect of the pathophysiology of depression. Several decades ago, Janowsky *et al.*³⁷ introduced the "cholinergic-adrenergic hypothesis" of depression and mania. They postulated that dysfunctions of the cholinergic-adrenergic balance might be associated with the pathophysiology of mood disorders. Although no evidence for the association between 19 cholinergic genes and BPD was found,³⁸ other evidence supports the role of this system in mood disorders. For instance, rats bred selectively for

increased sensitivity of muscarinic receptors demonstrated behaviors that are similar to those seen in patients with depression, such as lethargy, anhedonia, and behavioral despair.³⁹ In humans, enhanced cholinergic activity induced a worsening of symptoms in patients with unipolar depression.³⁷ Furthermore, neuroendocrine and pupillary responses to cholinergic activity are augmented in depressed subjects⁴⁰ and decreased in manic subjects.⁴¹ Improvement in mania with lithium and valproate is linked with normalization of pupillary responses.⁴¹

In addition, a recent positron emission tomography imaging study reported reduced muscarinic type 2 receptor binding in the anterior cingulate cortex in subjects with BPD.⁴² Further supporting the importance of the role of the cholinergic system in BPD is the fact that small, controlled trials of physostigmine, a short-acting cholinesterase inhibitor, led to rapid but only temporary decreases in symptoms of mania after single or multiple intravenous injections.^{43,44} A more recent study found that the long-acting cholinesterase inhibitor donepezil had rapid antimanic effects. In this open case series, donepezil (5–10 mg/day) was added to ongoing mood-stabilizer treatment and led to significant improvement in 6 of 11 patients with treatment-resistant mania.⁴⁵ However, a recent 6-week, double-blind, placebo-controlled trial failed to find that adjunctive donepezil (5–10 mg/day) was effective in the treatment of refractory manic symptoms.⁴⁶ It is possible that the small size of the sample (12 subjects randomized) could have led to a false-negative result, although YMRS scores at the endpoint were significantly higher in the donepezil group than the placebo group.

Until recently, only a handful of uncontrolled studies have suggested that anticholinergic drugs might have antidepressant efficacy. The antidepressant effects of tricyclic antidepressants were believed to be largely due to their anticholinergic properties. Earlier work by Kasper and colleagues⁴⁷ described the antidepressant properties of the anticholinergic drug biperiden in 10 severely depressed inpatients. More recently, Furey and Drevets⁴⁸ reported on 2 studies that unexpectedly found that the antimuscarinic drug scopolamine had antidepressant properties in subjects with unipolar and bipolar depression; these effects were rapid, occurring within 3 to 5 days. In the first of the 2 studies, 4 testing sessions were performed in random order under double-blind conditions, during which subjects received a 15-minute intravenous infusion of a saline placebo and 3 doses of scopolamine hydrobromide (2.0, 3.0, and 4.0 $\mu\text{g}/\text{kg}$). The second study involved 7 sessions in

which subjects received a 15-minute intravenous infusion of a placebo saline solution or scopolamine hydrobromide (4.0 $\mu\text{g}/\text{kg}$). The number of subjects with BPD was not specified in the first study, but there were 9 subjects with BPD in the second study. Analysis indicates that patients with BPD and major depressive disorder separately showed significant reductions in Montgomery-Asberg Depression Rating Scale (MADRS) scores when the endpoint was compared with the baseline. The authors reported that the antidepressant effects seen in the study with scopolamine were not simply due to euphoria; previous reports had suggested that anticholinergic drugs had this property.⁴⁹ In this study, only 1 patient developed euphoria on scopolamine. Furthermore, no increase in YMRS scores occurred in patients with BPD during scopolamine treatment when the baseline was compared with the study endpoint. In animals, scopolamine was reported to produce a significant dose-dependent decrease in prepulse inhibition, but it had no effect on startle amplitude.⁵⁰

Because anticholinergic side effects are a common complaint and reason for discontinuing tricyclic antidepressants in depressed patients, novel compounds currently in development that target the cholinergic system would need to factor in this potential problem. Further controlled short- and long-term studies are warranted to determine the efficacy, safety, and tolerability of anticholinergic compounds in mood disorders.

Nicotinic Acetylcholine Receptor (nAChR) System

The nAChR system is one of the best characterized neurotransmitter systems. To date, 12 neuronal nAChR subunits have been identified ($\alpha 2$ –10 and $\beta 2$ –4).⁵¹ The different pentameric nAChR subtypes can result from these subunit combinations and are distinguished on the basis of their affinities for nicotine (low or high) and other nAChR ligands. The nAChRs expressed in the mammalian brain with low affinity for the nicotine receptor appear to be $\alpha 7$ homomers, whereas those with a high affinity for nicotine have primarily $\alpha 4$ and $\beta 2$ subunits.⁵² A link between nicotine and depression has been suggested by epidemiological studies of smokers.⁵³ In animals, nicotine has been reported to have mood-elevating properties (hedonic), and its withdrawal induces an anhedonic state.⁵⁴ Indirect evidence for the involvement of nAChRs in depression was provided by the Flinders sensitive line, a genetic animal model of depression in rats that could be reversed by nicotine treatment.⁵⁵ Similarly, nicotine has been found to have antidepressant-like properties

in a learned helplessness test in rats.⁵⁶ Cytisine, a partial agonist of high-affinity nAChRs (a partial agonist of $\alpha 4/\beta 2$ and a full agonist at $\alpha 3/\beta 4$) was recently found to have antidepressant-like properties in male C57BL/6J mice.⁵⁷

Evidence for the involvement of the nicotinic system in BPD includes the fact that mRNA levels of $\alpha 7$ (located at chromosome 15a13-14) and $\alpha 7$ -like genes from the postmortem prefrontal cortex were significantly expressed in the postmortem tissue of subjects with BPD, but not in postmortem tissue of patients with schizophrenia or healthy controls.⁵⁸

In a recent 4-week, double-blind study, 11 nonsmokers with depressive symptoms (Center for Epidemiological Studies Depression Scale ≥ 10) were randomized to either transdermal nicotine (3.5–7.0 mg/day) or placebo. Nicotine induced significant antidepressant effects in comparison with placebo at day 8 but not on days 21 and 28. Reported side effects were infrequent and minimal.⁵⁹ These data appear to indicate that nicotine could play a role in major depression; however, the use of chronic nicotine as a standard treatment for depression is limited by obvious health risks and its side-effect profile (eg, nausea and sympathomimetic actions). The unwanted side effects are probably mediated through peripheral nicotinic receptors, and for that reason, studies with nicotinic subtype inhibitors are underway.

SIB-1508Y is a selective $\alpha 4/\beta 2$ nAChR agonist and has been found to have antidepressant-like properties in the learned helplessness model of depression in rats.⁶⁰ As with fluoxetine and imipramine, a dose-dependent study of subchronic treatment with SIB-1508Y reversed the escape deficit in the learned helplessness model, and this effect was still apparent 1 week later.

In terms of nicotinic antagonists, a previous study found that comorbid BPD was improved in 2 Tourette's syndrome patients treated with mecamylamine (2.5–7.5 mg/day). Mecamylamine blocks nicotinic receptors and was noted to have mood-stabilizing properties in these 2 patients; manic symptoms became apparent only upon cessation of mecamylamine treatment.⁶² Furthermore, a more recent study also found mecamylamine to have antidepressant and mood-stabilizing properties.⁶³ In this 8-week, double-blind, placebo-controlled trial, mecamylamine (2.5 to 7.5 mg/day) significantly decreased sudden mood changes in children and adolescents (8–17 years old) with Tourette's disorder and other comorbid disorders (attention deficit hyperactivity disorder, obsessive-compulsive disorder, and hypomania). In a completer's analysis, significant differences that favored mecamylamine over placebo

in the comorbid major depression group included "irritable," "sudden mood changes," "inattention," "restless" or hyper," "tense, anxious, nervous," and "impulsive." In the hypomania comorbid group, significant differences that favored mecamylamine over placebo included "restless or hyper" and "depressed or uninterested in most things." Although there are limitations with the aforementioned reports (including small sample size, overlapping comorbid diagnoses, and not direct testing in patients with BPD), the preliminary nature of the data indicating beneficial improvement of symptoms commonly seen in BPD with mecamylamine suggests that controlled trials with selective inhibitors of nAChRs in patients with mood disorders should be considered. These results complement the preclinical findings of "antimanic-like properties," in that mecamylamine attenuates both ephedrine-induced⁶⁴ and quinpirole-induced hyperactivity in rats.⁶⁵

In addition, mecamylamine was found in a dose-response study to significantly decrease immobility time the FST and tail suspension test at the dose of 1.0 mg/kg without altering baseline locomotor activity. These effects appear to be dependent on both $\beta 2$ and $\alpha 7$ subunits of the nAChR, as mice lacking these subunits failed to show evidence of the antidepressant-like properties⁶¹. Similarly to the opiate agonists, the potential for abuse and/or withdrawal symptoms from these types of compounds needs further study.

Melatonin and Serotonin (5-HT_{2C} Receptor) System

The pineal hormone melatonin produces most of its biological effects via G protein-coupled melatonin receptors (MT1 and MT2). In mammalian tissues, these receptors are particularly expressed in the brain. The cyclical nature of BPD, the varied fluctuations in its symptomatology, and the existence of disturbed sleep-wake rhythms all suggest that dysfunction of the circadian system may underlie the pathophysiology of this disorder. Supersensitivity of the melatonin-suppressing effects of light has also been reported in patients with BPD, in nonaffected offspring of probands with BPD, and in monozygotic twins discordant for BPD.^{66–68} However, Nurnberger and colleagues⁶⁹ did not confirm that melatonin suppression by light occurred in euthymic bipolar patients. Thompson and colleagues⁷⁰ found a significant association of the δ 502–505 polymorphism in GPR50 (also known as H9, melatonin-related receptor, or ML1X and located on Xq28) and susceptibility to BPD in a population from the Southeast Scotland. However, this finding

was not replicated in a Northern Swedish association sample.⁷¹

Interestingly, low doses of both lithium and valproate have been reported to reduce melatonin light sensitivity but not its overall synthesis in healthy volunteers.^{72,73} There are no controlled studies with melatonin in patients with BPD. Case reports and series indicate mixed results.^{74,75}

More recently, the availability of agomelatine, a potent agonist of melatonin MT1 and MT2 receptors, has allowed researchers to test the relevance of melatonin system treatments for mood disorders. However, agomelatine is not selective for MT1 and MT2, as it is also a 5-HT_{2C} antagonist; the latter property has also been implicated in the mechanism of action of atypical antipsychotic drugs with thymoleptic properties.⁷⁶ In vivo studies indicate that agomelatine increases both norepinephrine and dopamine in the frontal cortex. In addition to increasing these neurotransmitters, chronic agomelatine treatment (3 weeks) resulted in increased cell proliferation and neurogenesis in the ventral dentate gyrus as well as increased survival of these newly formed cells.⁷⁷ Furthermore, similar to lithium,⁷⁸ agomelatine is able to resynchronize a disrupted circadian rhythm and has circadian phase-advancement properties.^{79,80} Agomelatine is effective in animal models of depression (specifically, in the FST, chronic mild stress test, and learned helplessness model)^{81,82} and anxiety (the social interaction test and Vogel conflict test).⁸³

In 3 large, multicenter, multinational, placebo-controlled, short-term studies in major depression, agomelatine was found to be a clinically effective and well-tolerated antidepressant.^{84–86} In the study by Loo and colleagues,⁸⁴ some patients met criteria for bipolar II disorder (depressed); an analysis was not presented separately for patients with this type of diagnosis. Agomelatine appears to improve sleep quality and ease of falling asleep, as measured subjectively in depressed patients.⁸⁷ Agomelatine also shows a low liability for hypomania or mania in the several studies conducted to date,⁸⁸ which might explain the impetus to study it in BPD.

In a recent study, 21 patients with bipolar I disorder who were experiencing a major depressive episode and had a 17-Item Hamilton Depression Scale score of ≥ 18 were studied. All patients received agomelatine (25 mg/day) for 6 weeks with a possible extension of up to 46 weeks in combination with either lithium ($n = 14$) or valpromide ($n = 7$). According to intent-to-treat data, 81% of patients met criteria for marked improvement at the 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 6 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.⁸⁹ One interesting characteristic of the drug is that apparently its abrupt cessation does not result in discontinuation symptoms.⁹⁰

Glutamatergic System

Increasingly, the glutamatergic system is being recognized as a likely contributor to impairments in brain neuroplasticity and cellular resilience observed in patients with BPD. The preclinical evidence supporting the role of glutamate in the pathophysiology of depression or mechanism of action has been summarized elsewhere.^{91–93} 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 such as synaptic plasticity, learning, and memory.^{94–97} 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 types of compounds are neuroprotective in humans with ischemic/traumatic or neurodegenerative disease is still pending.

Several of the glutamatergic compounds being studied as neuroprotective agents either have been or are now undergoing testing in “proof-of-concept” studies in patients with severe mood disorders.^{91,98} The glutamatergic modulators that are being developed target either the glutamate receptors [*N*-methyl-D-aspartate (NMDA), AMPA, and 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 by enhancing AMPA throughput is thought to be involved in acute antidepressant response, whereas 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.

Glutamate Release and AMPA Trafficking Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is a blood-brain-penetrant glutamatergic modulator with neuroprotective and anticonvulsant properties. Riluzole is the only drug approved by the FDA for the treatment of the degenerative motor-neuron disease amyotrophic lateral sclerosis. There is mounting evidence that it has multiple effects on the glutamatergic system, including inhibition of glutamate release, enhancement of AMPA trafficking by increasing membrane insertion of AMPA subunits glutamate receptor type 1 (GluR1) and glutamate receptor type 2 (GluR2),⁹⁹ and glutamate reuptake.^{91,99,100} Riluzole is also known to stimulate the synthesis of growth factors, including brain-derived neurotrophic factor (BDNF) in cultured mouse astrocytes,¹⁰¹ and was recently shown to have antidepressant-like properties in animal models (G. Sanacora, unpublished data, 2008).

Several clinical studies have been conducted with riluzole. It was found to have antidepressant effects in patients with unipolar depression^{102,103} as well as bipolar depression.¹⁰⁴ Overall, riluzole was well tolerated in these trials. These preliminary results need to be confirmed in controlled studies. In mice, pretreatment with 10 mg/kg riluzole, but not 3 mg/kg riluzole, moderately reduced amphetamine-induced hyperlocomotion but not dizocilpine-induced hyperlocomotion.¹⁰⁵ This characteristic suggests that it might have “antimanic-like” properties, but more studies are needed to confirm this.

Inotropic Glutamate Receptors Three subgroups of glutamatergic ion channels have been identified on the basis of their pharmacological ability to bind different synthetic ligands: NMDA, AMPA, and kainate receptors.

NMDA Receptor Complex Data from preclinical and clinical investigations support the concept that the NMDA receptor complex may play a major role in the pathophysiology of mood disorders and the mechanism of action of antidepressants and possibly mood stabilizers (reviewed by Zarate *et al.*⁹¹). NMDA receptor antagonists (eg, dizocilpine and 2-amino-7-phosphonoheptanoic acid) as well as an AMPA receptor potentiator have been shown to have antidepressant properties in several animal models of depression and to induce neurogenesis in the brains of rats (reviewed by Zarate *et al.*⁹¹ and Cameron *et al.*¹⁰⁶). The next section summarizes studies investigating a partial glycine receptor agonist and NMDA antagonists in patients with mood disorders.

D-Cycloserine D-Cycloserine, an antibiotic used in the treatment of tuberculosis, is a partial agonist of the glycine recognition site of the NMDA receptor. In terms of evidence for its “antimanic properties,” only preclinical data have been published. D-Cycloserine was found to inhibit the hypermobility induced by methamphetamine but not that induced by apomorphine¹⁰⁷ and to decrease aggressiveness in the resident-intruder test.¹⁰⁸ In humans, D-cycloserine is currently being tested in bipolar depression in a trial supported by the Theodore and Vada Stanley Foundation. A recent study found it to be ineffective in treatment-resistant depression.¹⁰⁹ However, in addition to the limitations of this study as acknowledged by the authors (eg, unevenness in treatment-resistance criteria and concomitant medications), it is notable that in animal studies, a single dose of D-cycloserine elicited a dose-dependent reduction in immobility in the Porsolt swim test, whereas multiple doses did not.¹¹⁰ The investigators surmised that chronic administration of NMDA glycine partial agonists produced a behavioral tolerance putatively through adaptation of the NMDA receptor complex.

Memantine Memantine is a noncompetitive NMDA antagonist with both anticonvulsant and neuroprotective properties, and it is FDA-approved for the treatment of Alzheimer’s disease. Memantine is “use-dependent,” in that it blocks the NMDA receptor-associated ion channel only when the channel is open for long periods, as occurs in states of excitotoxicity. Consequently, the problematic effects of pathological concentrations of glutamate are prevented to a greater extent than the effects of physiological concentrations, which are relatively spared with memantine.^{111,112} Memantine is a fairly selective NMDA receptor antagonist at doses of 5 to 20 mg/day with negligible affinity for other receptors that have been implicated in antidepressant action.

Memantine has antidepressant-like effects when used alone¹¹³ or synergistically with imipramine¹¹⁴ in the FST in rats. Although memantine showed antidepressant-like effects in preclinical studies, in humans at the doses tested (up to 20 mg/day), it was found to be devoid of significant antidepressant or anti-anxiety effects in a double-blind, placebo-controlled trial in patients with major depression.¹¹⁵ Although no significant antidepressant effects were found within this study, it does not disprove the possibility that higher doses of memantine, augmentation strategies, or its use in different populations (eg, in BPD) may result in positive effects.

A recent open-label study involving 8 patients with major depressive disorder suggests that higher doses of memantine might be beneficial for some.¹¹⁶ In addition, a recent case series involving 2 patients indicated that memantine at doses of 10 to 20 mg/day improved depressive symptoms and cognitive performance in patients with BPD when added to existing mood-stabilizer therapy.¹¹⁷ Another small, open-label trial found that memantine had beneficial effects in hyperactivity and irritability in children with pervasive development disorders; these symptoms are often seen in patients with BPD.¹¹⁸ However, although this finding implies that memantine could be effective in treating the core symptoms of mania, it does not offer additional support for considering its further study in BPD. Another controlled study is investigating its use as an augmentation therapy in patients with bipolar depression who have an incomplete response to lamotrigine.

In terms of “antipsychotic-like” properties in animal models, memantine has been shown to disrupt prepulse inhibition of acoustic startle in rats.¹¹⁹ However, caution should be used with this information as NMDA antagonists, even those of low affinity, may have a propensity to induce psychosis, especially if used at high doses or in individuals prone to develop psychosis. Furthermore, memantine at high doses has been reported to induce seizures in kindled rats.¹²⁰

Ketamine In contrast to the evidence suggesting that memantine does not possess antidepressant effects in patients with major depression, 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 (unipolar) depression.^{98,121} The effects noted in the latter study were rapid (within 2 hours), 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.

AMPA Receptors AMPA receptors are ionotropic receptors implicated in learning and memory that 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 the AMPA receptors indirectly by slowing the receptor desensitization rate and/or deactivation in the presence of an agonist (eg, AMPA and glutamate; see Borges and Dingledine¹²² and Bleakman and Lodge¹²³ for reviews). Positive modulators of these receptors, the AMPAkinases, allosterically produce positive modulation of these receptors. These compounds are under active investigation as treatments for cognition, depression, anxiety, stroke, and Parkinson’s disease (reviewed by Black¹²⁴). Chronic treatment with traditional antidepressants increases the expression of AMPA receptors in hippocampal membranes¹²⁵ and the phosphorylation of AMPA receptor subunits.¹²⁶

LY392098, an ARP, was found to have “antidepressant-like” properties in the FST and in the tail suspension test. LY392098 alone dose-dependently reduced immobility in a manner similar to that of classic antidepressants, and at subthreshold doses, it potentiated the antidepressant effects of conventional antidepressants.¹²⁷ In contrast to conventional antidepressants, this group of compounds does not affect the extracellular concentration of monoamines.¹²⁸ In primary neuronal cultures, LY392098 increased BDNF mRNA,¹²⁹ which has been implicated in the mechanism of action of many currently available antidepressants.^{130,131} Another ARP that is being investigated in depression is S18986, which has also been reported to increase BDNF expression.^{129,132}

In terms of the effects of standard treatments for BPD (ie, lithium, valproate, and lamotrigine) on AMPA receptors, those agents with a predominantly antidepressant profile, namely, lamotrigine and riluzole, significantly enhanced the surface expression of GluR1 and GluR2 in a time- and dose-dependent manner in cultured hippocampal neurons. In contrast, the predominantly antimanic agents lithium and valproate significantly reduced surface expression of GluR1 and GluR2.^{99,133} These findings imply that regulation of GluR1/2 surface levels and function may be involved in the different clinical profile of anticonvulsants and suggest that drugs that mimic these biochemical effects might have a similar therapeutic role.

Because AMPA potentiators appear to have antidepressant-like properties (as discussed previously), it is possible that AMPA receptor antagonists could have antimanic effects. The first selective AMPA receptor antagonists to be identified were quinoxalinedone derivatives such as 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide, which

is an AMPA receptor antagonist at the glutamate recognition site of the receptor. In contrast to earlier AMPA antagonists that blocked the AMPA recognition site, more recent ones such as 2,3-benzodiazepines (eg, GYKI 52466) block AMPA receptors via an allosteric site on the receptor-channel complex.¹³⁴ At present, the GYKI 52466 analog talampanel (GYKI 53773; LY 300164) is undergoing phase III clinical trials. Talampanel, an anticonvulsant, was well tolerated in earlier clinical trials, but sedation may occur, especially with initial dosing (reviewed by Rogawski¹³⁵).

8-Methyl-5-[4-(*N,N*-dimethylsulfamoyl)phenyl]-6,7,8,9-tetrahydro-1*H*-pyrrolo[3,2-*b*]-isoquinoline-2,3-dione-3-*O*-(4-hydroxybutyric acid-2yl)oxime (NS 1209; SPD502) is a structurally novel, water-soluble, competitive AMPA receptor antagonist with good central nervous system bioavailability.¹³⁶ NS1209 has been well tolerated in phase I/II clinical trials and is being evaluated for the treatment of refractory status epilepticus (reviewed by Rogawski¹³⁵).

Metabotropic Glutamate Receptors (mGluRs)

The mGluRs comprise a family of 8 receptor subtypes (mGluR1 to GluR8) that are classified into 3 groups on the basis of their sequence homology, coupling to second messenger systems, and agonist selectivity. Group I mGluRs (mGluR1 and mGluR5) are coupled to the phospholipase C signal transduction pathway. Group II (mGluR2 and mGluR3) and III (mGluR4 and mGluR6 to mGluR8) receptors are both coupled in an inhibitory manner to the adenylyl cyclase signal transduction pathway, which is generally involved in the regulation of the release of glutamate or other neurotransmitters [eg, γ -aminobutyric acid (GABA)], depending on synaptic localization.¹³⁷ The mGluRs are involved in the early phase of memory formation and the mechanism of long-term depression.^{138–140} The Group I mGluR5 antagonists 2-methyl-6-[phenylethynyl]-pyridine and [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine have shown antidepressant-like activity in the modified FST in rats,¹⁴¹ in the tail suspension test in mice,¹⁴¹ and in olfactory bulbectomized rats.¹⁴² Furthermore, 2-methyl-6-[phenylethynyl]-pyridine treatment was recently found to increase the hippocampal mRNA level.¹⁴³ The mGluR1 antagonist [3-ethyl-2-methyl-quinolin-6-yl]-(4-methoxy-cyclohexyl)-methanone methanesulfonate was active in the modified FST in rats and in the tail suspension test in mice.¹⁴⁴

The mode of antidepressant-like activity of mGluR1 or mGluR5 antagonists is uncertain; some

have suggested that inhibitors of mGluR5 might produce a final effect that is similar to that evoked by NMDA antagonists, which are known to display antidepressant-like activity (as discussed previously). It remains unclear whether mGluR5 antagonists will be safe enough to use clinically. Acamprosate is a weak mGluR5 antagonist; studies conducted with it in BPD have been presented at scientific meetings and reportedly did not show efficacy. Several possibilities exist for the lack of improvement with this agent, including its weak affinity for different glutamate receptors and its poor oral absorption. Studies conducted with the non-benzodiazepine anxiolytic fenobam, a potent and selective mGluR5 antagonist, were discontinued because of psychostimulant effects that occurred with its use.¹⁴⁵ More recently, the mGluR5-positive allosteric modulator 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide was found to be a brain penetrant and to reverse amphetamine-induced locomotor activity and amphetamine-induced deficits in prepulse inhibition in rats; these 2 models were thought to be sensitive to antipsychotic treatment.¹⁴⁶ Should this compound result in an antipsychotic drug for clinical use, it is likely that it will be used clinically in patients experiencing a manic episode. Unfortunately, no preclinical data have been published on whether it has an antidepressant profile.

Group II mGluR2 and mGluR2/3 are negatively linked to the adenylyl cyclase signal transduction pathway and decrease glutamate release, especially under conditions of glutamate excess in the synapse; moreover, they regulate glutamate transmission by postsynaptic mechanisms. Group II mGluRs agonists (eg, LY341495) dose-dependently decreased the immobility time of mice in the tail suspension test and reduced immobility time and increased swimming behavior without affecting climbing behavior in rats.¹⁴⁷ Moreover, MGS-0039 has been reported to be effective in the learned helplessness model of depression¹⁴⁸ and to increase cell proliferation in the adult mouse hippocampus.¹⁴⁹ Activation of AMPA receptors has been reported to be responsible at least in part for the antidepressant-like activity of group II mGluR antagonists; the AMPA antagonist 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide blocked the antidepressant-like activity of MGS-0039 in the tail suspension test in mice.¹⁵⁰

A type 2 mGluR receptor agonist, LY 354740, was recently tested in patients with panic disorder. LY354740 failed to separate from placebo in the primary panic measures, whereas paroxetine did. Although the MADRS scale was collected at

baseline and at week 9, no MADRS score was reported for these time points. The compound was generally well tolerated; the most commonly reported adverse events were gastrointestinal complaints (nausea, diarrhea, and stomach pain) and headache. Two of 18 subjects discontinued the compound because of an allergic reaction.¹⁵¹ A multicenter trial of LY35470 for the treatment of panic disorder was suspended because preclinical studies showed convulsions in mice.¹⁵² No noticeable antipsychotic effects were noted with LY35470, as indicated by its inability to block the increase in Positive and Negative Syndrome Scale scores due to ketamine infusion.¹⁵³ Unfortunately, no information is available in depression paradigms.

Pilc and colleagues demonstrated that a selective group III mGluR agonist ([1*S*,3*R*,4*S*]-1-aminocyclopentane-1,3,4-tricarboxylic acid) and an mGluR8 agonist ([*RS*]-4-phosphonophenylglycine) for this receptor resulted in antidepressant-like effects in the FST in rats.¹⁵⁴ Additional proof for the involvement of group II mGluRs comes from the work of Cryan and colleagues,¹⁵⁵ who showed that mGluR7 knockout in mice produced antidepressant-like effects in the FST and in the tail suspension test in mice. Palucha and colleagues¹⁵⁶ similarly reported the antidepressant-like effects of group III mGluR agonists in the behavioral despair test.

No group III mGluR agonists are yet at the clinic stage for testing. Although there have been no studies with these compounds in animal models of mania, the mGluR5 antagonists and group II mGluR antagonists seem to be very promising compounds, with considerable potential antidepressant-like activity.

HPA Axis

Dysfunction of the HPA axis has been well described in bipolar depression. Hypercortisolemia may be central to the etiopathogenesis of both the depressive symptoms and the neurocognitive deficits observed in BPD. Strategies to better regulate 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 depression include both cortisol synthesis inhibitors (aminoglutethimide, ketoconazole, and metyrapone) and corticosteroid receptor antagonists (mifepristone),¹⁵⁷ hydrocortisone and dexamethasone,^{158,159} and dehydroepiandrosterone (DHEA; reviewed by Quiroz *et al.*¹⁶⁰). Treatment

with glucocorticoid synthesis inhibitors (eg, ketoconazole and metyrapone), the corticotropin releasing factor type 1 (CRF 1) receptor antagonist R-121919, and DHEA has been observed to ameliorate depressive symptoms in patients with unipolar depression (reviewed by Quiroz *et al.*,¹⁶⁰ Jahn *et al.*,¹⁶¹ Zobel *et al.*,¹⁶² and Schmidt *et al.*¹⁶³). Clinical development of R-121919 was terminated because of its association with abnormal liver function tests.¹⁶⁴ DHEA has also been reported to be associated with a high propensity to induce mania.¹⁶⁵

The only antiglucocorticoids that have been tested in BPD are ketoconazole and mifepristone. Ketoconazole (up to 800 mg/day) was given as an add-on therapy in 6 depressed patients who had a diagnosis of treatment-resistant BPD.¹⁶⁶ 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 with ketoconazole preclude its use on a chronic basis for mood disorders.

Only 1 placebo-controlled study of an antiglucocorticoid for bipolar depression has been performed. Mifepristone (RU-486) is a nonselective antagonist of the glucocorticoid receptor that has been reported to have antidepressant and antipsychotic properties in patients with psychotic depression¹⁵⁷ (reviewed by Quiroz *et al.*¹⁶⁰), although a recent letter to the editor indicates that 2 large phase III studies failed to find significant antipsychotic or antidepressant effects.¹⁶⁷ Animal studies suggest that glucocorticoid receptor numbers are increased rapidly (within hours) after the administration of RU-486, which may restore normal feedback, thus “resetting” the HPA axis. In a recent double-blind, placebo-controlled crossover study, Young and colleagues¹⁶⁸ compared mifepristone (600 mg) to placebo in 20 subjects with bipolar depression. Over the course of the 6-week study, neurocognitive and neuroendocrine function and mood symptoms were measured. The study found not only benefits in depressive symptoms with mifepristone but also benefits in cognitive functioning, specifically in spatial memory. If mifepristone is found to have a beneficial effect in BPD, its use will most likely be limited to acute depressive episodes; long-term treatment would have significant side effects, including the potential for adrenal insufficiency and hepatic injury.¹⁶⁹ In addition, mifepristone has significant antiprogesterone effects, and its chronic use could lead to fatigue, hot flashes, gynecomastia/breast tenderness, and

endometrial hyperplasia.¹⁷⁰ A large controlled study with mifepristone in bipolar depression is currently underway (NCT0035912 by Alan Young at the University of British Columbia). Examples of other GR antagonists under development are provided in Table 1.

CRF 1 Receptor Antagonists A number of small-molecule CRF 1R antagonists have been evaluated with in vivo paradigms in animal models to attenuate CRF-induced adrenocorticotrophic hormone (ACTH) release.¹⁷¹ Several classes of CRF 1R inhibitors have been identified (Table 1; see Saunders and Williams¹⁷¹ and Holmes *et al.*¹⁷² for reviews). In

preclinical studies, CRF 1 antagonists diminished CRF-induced ACTH release as well as CRF-induced cyclic adenosine monophosphate production (see Saunders and Williams¹⁷¹ for a review). In an open-label study, R-121919 reduced anxiety and depressive symptoms in patients with major depression.¹⁶² Some companies have discontinued clinical development of these compounds because of laboratory abnormalities; others are still being developed.

Antalarmin, a novel pyrrolopyrimidine compound, in oral doses of 20 mg/kg in primates significantly reduced CRF-stimulated ACTH release as well as the pituitary-adrenal, sympathetic, and adrenal medullary responses to stress. It also reversed

Table 1. Examples of Candidate Drugs for the Treatment of Bipolar Disorder.

System	Drug/Compound*
Dynorphin opioid neuropeptide system	Kappa opioid receptor antagonists: questionable antidepressant effects Kappa opioid receptor agonists: questionable antimanic effects, pentazocine (Talwin; partial agonist for kappa opiate receptor)
Cholinergic system	Anticholinergic: scopolamine (antimuscarinic) and donepezil (cholinesterase inhibitor)
Nicotinic acetylcholine receptor	Cytisine (partial agonist of $\alpha 4/\beta 2$ and a full agonist at $\alpha 3/\beta 4$); SIB-1508Y ($\alpha 4/\beta 2$ agonist); mecamylamine (nicotinic antagonist)
Melatonin and serotonin system	Agomelatine (melatonin MT1 and MT2 agonist and 5-HT2C antagonist)
GSK	GSK inhibitors: zinc, indirubines, maleimides, hymenialdesine, paullones, thiazolidones, synthetic phosphorylated peptide, and azole derivatives
PKC	PKC inhibitors: tamoxifen, LY33531, ruboxistaurin, rottlerin, indolocarbazoles, UCN-01, CGP41251, PKC412, bisindolylmaleimides, balanol, indolylindazolylmaleimides, and aprinocarsen
Arachidonic acid metabolism	Celecoxib (COX-2 inhibitors)
Glutamate release and AMPA receptor	Riluzole (inhibitor of glutamate release, enhancer of AMPA trafficking and glutamate synaptic clearance)
NMDA receptor complex	D-Cycloserine (partial agonist glycine site); NMDA antagonist: memantine and ketamine
AMPA receptor potentiators	Benzoylpiperidone (aniracetam), benzoylpyrrolidines (ampakines), arylpropylsulfonamides (LY392098, LY451616), and S18986
mGluR	MPEP, MTEP, EMQMCM, and CDPPB (group I mGluR5 antagonists); LY341495 and MGS-0039 (group II mGluR2s); GluR2/3 agonists; ACPT-I and RS-PPG (III mGluR agonists)
Glucocorticoid synthesis	Glucocorticoid synthesis inhibitors: ketoconazole, aminoglutethimide, and metyrapone
GR II receptor	GR II receptor antagonists: mifepristone (RU-486), ORG 34517, ORG 34850, ORG 34116, AL082D06, and cyproterone acetate
CRF 1 receptors	CRF 1R antagonists: peptides (astressin and α -helCRF) and small-molecule nonpeptides (CP-154526, antalarmin, DMP695, DMP696, CRA1000, R-121919, SSR125543, NBI 35965, and NBI 27914)
Bcl-2 enhancer	Pramipexole

Abbreviations: 5-HT2C, 5-hydroxytryptamine (serotonin) receptor 2C; ACPT-I, [1S,3R,4S]-1-aminocyclopentane-1,3,4-tricarboxylic acid; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid Bcl-2, B cell lymphoma-2; CDPPN, 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide; COX, cyclooxygenase; CRF, corticotropin releasing factor; EMQMCM, [3-ethyl-2-methyl-quinolin-6-yl]-(4-methoxy-cyclohexyl)-methanone methanesulfonate; GC, glucocorticoid; GluR, glutamate receptor; GSK, glycogen synthase kinase; mGluR, metabotropic glutamate receptor; MPEP, 2-methyl-6-[phenylethynyl]-pyridine; MTEP, [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; NMDA, N-methyl-D-aspartate receptor; PKC, protein kinase C; RS-PPG, [RS]-4-phosphonophenylglycine.

* Drugs/compounds are at different stages of development; some may have been tested for proof of concept rather than for clinical use, and others at this time may not be usable on a long-term basis because of treatment-limiting side effects. Although valproate has plasticity-enhancing characteristics, it remains unclear whether they are due to valproate's ability to inhibit GSK-3 and histone deacetylase.

stress-induced inhibition of exploratory and sexual behaviors.¹⁷³ With the chronic stress model in mice, both antalarmin (10 mg/kg) and fluoxetine (10 mg/kg) significantly improved measures of physical state, weight gain, and emotional response in the light-dark test in comparison with stressed, untreated animals.¹⁷⁴ Antalarmin reduced swim-stress-induced ACTH response but did not show antidepressant-like effects in the FST.¹⁷⁵

CP-154,526, developed by Pfizer, has been evaluated in animal paradigms for anxiety. Like antalarmin, it has high brain-barrier penetrability, decreases synthesis of CRF in the paraventricular nucleus,¹⁷⁶ and shows antidepressant-like properties in the learned helplessness model of depression in rats.¹⁷⁷ SSR125543A, a 2-aminothiazole derivative that displays high affinity for human CRF R1 receptors, has shown efficacy in the FST model and in the chronic mild stress model in rats.¹⁷⁸ In addition, SSR125543A was able to reverse stress-induced suppression of neurogenesis in mice subjected to chronic mild stress,¹⁷⁹ and it has also been shown to reduce aggressive behaviors in male Syrian hamsters in the resident-intruder aggression test.¹⁸⁰ In other studies, CRA 1000, a nonpeptide pyrimidine CRF 1 antagonist, was found to reduce immobility in the learned helplessness paradigm in male Wistar rats.¹⁸¹ DMP696, developed by Dupont, is a selective, potent, and highly bioavailable nonpeptide CRF 1R antagonist. It has been tested in behavioral models of anxiety and is being tested in behavioral paradigms for depression.¹⁸²

B Cell Lymphoma-2 (Bcl-2) Enhancers As discussed previously, mood disorders are increasingly being found to be associated with problems in neuroplasticity and cellular resilience. Neurotrophic factors are known to promote cell survival largely by suppressing intrinsic, cellular apoptotic machinery. Cell survival appears to occur through the binding of these factors to membrane receptors and regulation of intracellular signal transduction pathways that can control apoptosis, including regulation of the Bcl-2 family of proteins. Bcl-2 is not only neuroprotective; it also exerts neurotrophic effects, promotes neurite sprouting and outgrowth, and promotes axonal regeneration. Recent studies have demonstrated that severe stress exacerbates stroke outcome by suppressing Bcl-2 expression¹⁸³; stressed mice expressed approximately 70% less Bcl-2 mRNA than unstressed mice after ischemia in a stroke model. Enhanced Bcl-2 expression appears to offset the potentially harmful consequences of stress-induced neuronal endangerment, and this suggests that up-regulation of Bcl-2 by pharmacological means may

have substantial value in the treatment of mood disorders.

Bcl-2 has traditionally been viewed as a “long-term neuroprotective protein”; however, Bcl-2 is also a major regulator of mitochondrial function, and there is increasing proof of the various roles that mitochondria play in modulating integrated central nervous system function. Thus, mounting evidence suggests that mitochondrial Ca²⁺ sequestration plays a key role in modulating the tone of synaptic plasticity in a variety of neuronal circuits and that regulation of mitochondrial function is likely to play an important role in regulating the synaptic strength of neuronal circuitry mediating complex behaviors. Indeed, it is quite possible that lithium’s antidepressant potentiating effects are due to its ability to robustly up-regulate Bcl-2. It is also noteworthy that pramipexole similarly up-regulates Bcl-2 in several brain areas¹⁸⁴ and has been shown to exert antidepressant effects in 2 small, double-blind, placebo-controlled trials in patients with bipolar depression.^{185,186} Future studies would have to test whether selective Bcl-2 enhancers without dopamine effects also have antidepressant effects in bipolar depression.

INTRACELLULAR PATHWAYS AND TARGETS WORTHY OF FURTHER STUDY IN BPD

GSK-3

GSK-3 is a serine/threonine kinase that is normally highly active in cells and is deactivated by signals originating from numerous signaling pathways (eg, the Wnt pathway, the phosphoinositide 3-kinase pathway, protein kinase A, and PKC).

Interest in GSK-3 is in line with contemporary theories of mood disorders that point to their association with impairments of neuroplasticity and cellular resilience; neuroimaging findings show regional reductions in brain volume corresponding at the tissue level to decreases in the number, size, and density of neurons and glia precisely in critical circuits purportedly involved in mood disorders. In general, increased activity of GSK-3 is proapoptotic, whereas inhibiting GSK-3 attenuates or prevents apoptosis. Lithium has neurotrophic and neuroprotective properties in rodent and cell-based models, and these effects are clinically suggestive of neuroprotection. Lithium may exert these neuroprotective effects in part by inhibiting GSK-3. More recent preclinical evidence implicates the modulation of GSK-3 in either the direct or

downstream mechanism of action of many other mood stabilizer and antidepressant medications currently being prescribed (see Gould and Manji¹⁸⁷).

Some of the behavioral effects of lithium may be due to inhibition of GSK-3. Pharmacological inhibition of GSK-3 attenuates D-amphetamine hyperlocomotion in rats, which is believed to represent, albeit imperfectly, an animal model of mania.¹⁸⁸ Furthermore, mice overexpressing a constitutively active form of GSK-3 β in the brain showed increased locomotor activity as well as decreased habituation in an open field. In support of this notion, we found antidepressant-like behavior in the FST and antimanic-like response to amphetamine following administration of the GSK-3 inhibitor AR-A014418.^{188,189} Thus, decreased expression of GSK-3 β resulted in attenuation of stimulant-induced locomotion, whereas its increased expression resulted in an endogenously high level of activity.

Proof-of-principle studies with selective GSK inhibitors are urgently needed in BPD to determine the relevance of this target. At present, no blood-brain-penetrant GSK-selective inhibitors are available for human use (Table 1).

PKC Signaling Cascade

PKC is highly enriched, has a heterogeneous distribution in the brain, and plays an important role in regulating neuronal excitability, neurotransmitter release, and long-term alterations in gene expression and plasticity. A considerable amount of biochemical data support the potential involvement of PKC and its substrates in bipolar patients and changes in PKC signaling pathways after treatment with lithium or valproate.^{190–195} These findings provide ample evidence that the PKC signaling pathway is clearly a target for the actions of 2 structurally highly dissimilar antimanic agents—lithium and valproate—and provide the impetus to test a PKC inhibitor in mania. Although best known for its anti-estrogenic properties, tamoxifen is also a potent PKC inhibitor, especially at high concentrations. In animals, tamoxifen has no effect on the resident-intruder test in males (an “animal model of mania”) or in the FST in mice¹⁹⁶ but does reduce amphetamine-induced hyperactivity in a large open field and amphetamine-induced phosphorylation of growth-associated protein 43.¹⁹⁷

In humans, tamoxifen was found to have significant antimanic effects. In a single-blind study, tamoxifen treatment significantly decreased manic symptoms in 5 of 7 patients enrolled in the initial trial.¹⁹⁸ In another recently completed double-blind, placebo-controlled trial with tamoxifen in patients

with bipolar mania, tamoxifen exhibited significant antimanic effects in doses as high as 140 mg/day as early as day 5 and throughout the 3 weeks of the trial.¹⁹⁹ The antimanic effect of tamoxifen was not the result of sedation. There was no increased risk of depression with tamoxifen compared to placebo in this short-term study. Whether tamoxifen is associated with an increased risk of depression if used on a long-term basis in patients with mood disorders is unknown.

Other studies conducted with tamoxifen also confirm the relevance of PKC inhibition in antimanic agents.^{200,201} Other drugs with PKC inhibitory effects include omega-3 fatty acids and verapamil, but these effects are very weak and perhaps in part explain why they have not been found to be consistently effective in BPD. With respect to the selectivity of tamoxifen's effects on PKC, it is important to re-emphasize that tamoxifen is also an anti-estrogen. It is possible that some of the antimanic effects seen with tamoxifen are attributable to estrogen receptor antagonism (see Goldstein²⁰¹). To our knowledge, the PKC line of research provides evidence for the first time in BPD drug development of a direct molecular target whose inhibition results in antimanic effects in humans. The role of PKC inhibition in bipolar depression or in long-term maintenance treatment is unknown at this time. Large controlled studies with selective PKC inhibitors in acute bipolar mania are warranted.

AA Cascade

Accumulating data suggest that an inflammatory process is involved in the pathophysiology of mood disorders. The enzymes that regulate the brain AA cascade have been implicated in BPD. AA functions as a key intermediary of second messenger pathways within the brain. It is released from membrane phospholipids via receptor/G protein–initiated activation of phospholipase A2. This action results in the release of AA from the cellular membrane and cyclooxygenase (COX)-mediated production of eicosanoid metabolites such as prostaglandins and thromboxanes. These metabolites mediate many subsequent intracellular and transynaptic responses.

Chronic treatment with lithium and valproate in rats selectively reduces the turnover rate in brain phospholipids of AA, which are believed to be hyperactive in mania.²⁰² In addition, lithium down-regulates the gene expression and protein levels of an AA-specific phospholipase as well as the protein levels of COX-2. Valproate decreases turnover of AA, protein levels of COX-1 and COX-2,²⁰³ and frontal cortex COX-2 mRNA.²⁰⁴ COX-2 also protects against neurotoxicity promoted by excessive concentrations

of glutamate. These findings suggest that the effects of mood-stabilizer therapies on cell membranes and specifically on AA turnover might be relevant to the mechanism of action of lithium and valproate.

Additional evidence for the involvement of the AA signaling pathway in BPD comes from other preclinical and clinical studies. Administration of the nonselective COX inhibitors indomethacin and piroxicam in rats prevented amphetamine-stimulated locomotor 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.²⁰⁵ In humans, celecoxib was also found to have antidepressant properties. In a 6-week, double-blind, placebo-controlled trial, Muller and colleagues²⁰⁶ found that celecoxib (400 mg/day), when added to reboxetine in patients with major (unipolar) depression, produced significant antidepressant effects in comparison with placebo. 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 the study endpoint.²⁰⁷ Notably, it remains unclear how brain-penetrant celecoxib actually is. 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.²⁰⁸

OTHER DRUGS BEING TESTED IN BPD

Modafinil is approved as a wake-promoting agent for the treatment of excessive daytime sleepiness in narcoleptic patients.²⁰⁹ The precise mechanism of action of modafinil is unknown, but it is believed to operate on multiple systems, including glutamate, GABA, hypocretin, and, to a lesser degree, dopaminergic and noradrenergic systems. More specifically, it is known to activate noradrenergic α 1 receptors, to increase phosphorylation of mitogen-activated protein kinase in cultured mouse cells, to decrease GABA release in the nucleus accumbens of rats, to weakly increase dopamine in the nucleus accumbens secondary to decreased GABA,²¹⁰ to increase the release of glutamate in the hippocampal formation and ventromedial and ventrolateral areas of the thalamus,

and to activate hypocretin-secreting neurons in the perifornical area. Modafinil is being increasingly used in mood disorders with apparent beneficial effects. In a 6-week, randomized, double-blind, placebo-controlled evaluation of modafinil (mean dose: 177 mg) in subjects with bipolar I or II depression who were inadequately responsive to mood stabilization with or without adjunctive antidepressant therapy (n = 87), there was greater baseline-to-endpoint change in modafinil versus placebo and from week 2 on between the groups.²¹¹ No manic switches were reported. In another study, Frye and colleagues (unpublished data reported by Post *et al.*²¹²) compared the adjunctive use of modafinil (100 or 200 mg in the morning for 3 weeks) with placebo in the treatment of patients with BPD and residual depressive symptoms, fatigue, or both. Modafinil was significantly more effective than placebo on a variety of measures, including the baseline-to-endpoint change on the Inventory for Depressive Symptoms, percentage response rate, remission rate, and clinical global impression improvement. Modafinil was not significantly associated with a treatment-emergent manic episode. One case report described a manic switch in a patient with treatment-resistant bipolar depression treated with modafinil,²¹³ and 2 cases of modafinil-induced irritability and aggression in 2 bipolar patients have been described.²¹⁴

A proprietary formulation of the nucleoside uridine, Uridine RG2417 (Repligen Corp.), a biological compound essential for the synthesis of DNA and RNA, is currently in development for the treatment of neuropsychiatric disorders and neurodegenerative diseases. A previous study suggested that RG2133, the prodrug of RG2419, had antidepressant-like effects in an animal model of depression. RG2417 was recently found to be efficacious in a phase 2a multisite study in bipolar depression. This was a multicenter study in which 84 patients received either RG2417 or placebo twice a day. Over the 6-week treatment period, patients receiving RG2417 demonstrated a statistically significant improvement in the symptoms of depression in comparison with those patients receiving placebo on the MADRS ($P = 0.03$) and a strong trend toward improvement on the Clinical Global Impression of Change in Bipolar Disorder Scale ($P = 0.06$). This study was conducted under a development agreement with the Stanley Medical Research Institute (study ID number NCT00322764; <http://www.medicalnewstoday.com/articles/88213.php>).

A neuronal L-type calcium channel modulator (MEM 1003, Memory Pharmaceuticals) was found to lack efficacy in acute mania in a phase 2a multisite study (study ID number NCT00374920;

<http://www.genengnews.com/news/bnitem.aspx?name=13780779>). In that study, approximately 80 subjects were randomized to receive MEM 1003 (120–360 mg/day) or placebo for 21 days.

CONCLUSIONS

By the criteria specified for this review article, a number of candidate targets were found that could result in putative treatments for BPD. These include (1) the purinergic system, (2) the dynorphin opioid neuropeptide system, (3) the cholinergic system (muscarinic and nicotinic systems), (4) the melatonin and serotonin (5-HT_{2C} receptor) system, (5) the glutamatergic system, and (6) the HPA axis as well as (7) GSK-3 protein, (8) PKC, (9) the AA cascade, and (10) other systems.

Drug development for BPD may occur through 1 of 2 approaches.⁹³ The first is through an understanding of the therapeutically relevant biochemical targets of currently effective medications; examples of this approach have been reviewed here and include the common targets of lithium and valproate, which are PKC and GSK-3 β . The investigation of PKC illustrates how this approach could lead to the development of therapeutics for BPD. In the first phase, the shared molecular targets of lithium and valproate were identified: in this case, PKC. Next, the therapeutic relevance of this finding was established in preclinical clinical studies and in biochemical studies in patients suffering from this disorder. Finally, and most notably, the relevance of this target was tested in humans; the end result was that the PKC inhibitor tamoxifen was found to result in antimanic effects in patients with bipolar mania.

The second path for drug development results from our 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. Newer “plasticity-enhancing” strategies that may be useful in the treatment of mood disorders include inhibitors of glutamate release, NMDA antagonists, and glucocorticoid receptor antagonists.

Finally, several points merit further discussion. First, the drugs/drug mechanisms reviewed here are potentially worthy of study in 1 pole of the illness, but it remains unclear whether they would be equally effective for the other pole of the illness or in maintenance treatment. Second, the proof-of-concept studies reviewed here are based on very small sample sizes, and additional study of these drugs is necessary in larger controlled trials before they can be

generalized to current clinical practice. Third, when one is deciding on a drug mechanism or target to pursue in drug development for BPD, consideration should be given to the following set criteria. Not doing so increases the risk of developing drugs that are not likely to succeed. For example, many lessons were learned when the GABAergic agents failed to demonstrate efficacy in mania; they were chosen and developed primarily on the presumptive drug mechanism alone (reviewed by Goodnick²¹⁵).

Enriched criteria for establishing target validation for further development in BPD have been proposed.^{130,191} These include (1) corroboration of a target at the protein and functional level; (2) observation with chemically dissimilar but clinically effective agents; (3) occurrence at a dose/plasma level and time frame consistent with clinical therapeutic effect; (4) localization to brain regions implicated in the neurobiology of the disorder under consideration; (5) when known, relevance to known pathophysiology; and (6) when possible, tethering to human genetic findings. Indeed, such a strategy was recently used in the development of the PKC inhibitors.²¹⁶

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DISCLOSURES

There is nothing to report.

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