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Putative Drugs and Targets for Bipolar Disorder

Carlos A. Zarate, Jr.[1] and **Husseini K. Manji**[1]

[1]Laboratory of Molecular Pathophysiology and Experimental Therapeutics, Mood and Anxiety Disorders Research Program, National Institute of Mental Health

Abstract

Current pharmacotherapy for bipolar disorder (BPD) 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 BPD is urgently needed. Promising drug targets and compounds for BPD worthy of further study involve the following systems: purinergic, dynorphin opioid neuropeptide, cholinergic (muscarinic and nicotinic), melatonin and serotonin (5-HT2C receptor), glutamatergic, hypothalamic-pituitary adrenal (HPA) axis have all been implicated. Intracellular pathways and targets worthy of further study include glycogen synthase kinase-3 protein, protein kinase C, arachidonic acid cascade.

Keywords

antidepressant; bipolar disorder; depression; glutamate; mania; plasticity; treatment

Bipolar disorder (BPD) is one of the most severe illnesses 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%, 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, hedonic and motoric drive over the course of the 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, 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 antimanic agents available for clinical use, although a sizable proportion of patients fail to response to or tolerate these treatments (2). However, for acute depressive episodes and for maintenance treatment, few treatments have proven to be effective; this is especially concerning 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 (MDD) achieved remission with an adequate trial of a standard antidepressant after approximately 10-14 weeks of treatment. For BPD depression, the use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased

Address correspondence to: Dr. Carlos A. Zarate, Jr., 10 Center Drive, Mark O. Hatfield CRC, Unit 7 SE, Rm. 7-3445, Bethesda, Maryland, 20892. Tel. (301) 451-0861, FAX (301) 402-9360, email: zaratec@mail.nih.gov.

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 based on 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 complexity of studying this illness (e.g. 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-October 2007) looking for examples of compounds or drugs that met one 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; (3) antidepressant-like properties in animal models *and* either (a) "antimanic-like" properties in animal models (8) or (b) antipsychotic-like properties either in humans or animal models of psychosis (e.g., 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 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 (muscarinic and nicotinic systems), (4) the melatonin and serotonin (5-HT2C receptor) system, (5) the glutamatergic system, and (6) the hypothalamic-pituitary (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, generalizability of such preliminary findings to current clinical practice patterns would be premature.

Systems Worthy of Further Study in Bpd

The purinergic system

Purines play an essential role in energy metabolism and are regulators of neurotransmission (ATP and adenosine); adenosine is a widespread neuromodulator acting mostly through adenosine-1 and -2A receptors (A1 and A2A). Uric acid is the ultimate step in the metabolism of the purinergic system. In the 19th century the 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, Cade 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 (10). Anumonye (1968) reported that remission in mania was associated with the increased excretion of uric acid (11). 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, two 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 eight weeks. Post-hoc comparisons showed significant improvement as early as day seven on the Young Mania Rating Scale (YMRS), and the difference between the two groups was also significant at endpoint (eight weeks). Side effects for the two groups were comparable. The second study was a four-week, double-blind, placebo-controlled study involving 150 subjects with acute bipolar mania. The study compared allopurinol (600 mg/day) to dipyridamole (200 mg/day) to placebo added-on 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.

The 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 three well-defined types of opioid receptors: μ, κ, and δ. All of these types of opioid receptors have been implicated to different degrees in major depression. A significant reduction (37-38%) of the prodynorphin mRNA expression levels in the amygdalohippocampal area and in the parvicellular 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 agonists such as U50,488 produce analgesia, diuresis, and show antipruritic activity (23). Selective kappa opiate antagonists are being explored for their effects in the treatment of a wide variety of conditions including cocaine addiction (24) and feeding behavior abnormalities (25), and have been proposed as a treatment for psychosis (26). Activation of kappa opiate receptors has depressogenic effects in both animals (27) and humans (28). Blockade of kappa opiate receptors results in antidepressant-like properties in animals (29). Recently, there is evidence of the antidepressant-like properties of the kappa opioid antagonist MCL-144B in the forced swim test (FST) (30). 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 (31,32).

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 (33). In this inpatient study, subjects received two 50 mg doses of pentazocine two hours apart. Symptoms of mania were reported to be reduced one hour after each dose—44% after the first dose and 41% one hour after the second dose—and were 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 intoxication (34), and because there have been reports that it induces symptoms of depression and "gloominess" in healthy volunteers (35). 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 (36). It is a naturally occurring hallucinogen identified to be a highly selective full kappa opioid receptor agonist (26). A recent study (27) 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 Salvinorin-A's mode of action will undoubtedly lead to a better understanding of the kappergic system in human brain function, as well as to the development of a series of novel compounds for potential therapeutic use in neuropsychiatric conditions (37). It should also be noted that the potential of abuse and/or withdrawal of these types of compounds will need to be further studied before they can be of clinical utility.

The cholinergic system

The cholinergic system has long been studied as an important aspect of the pathophysiology of depression. Several decades ago, Janowsky introduced the "cholinergic-adrenergic hypothesis" of depression and mania (38). 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 (39), 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 (40). In humans, enhanced cholinergic activity induced a worsening of symptoms in patients with unipolar depression (38). Furthermore, neuroendocrine and pupillary responses to cholinergic activity are augmented in depressed subjects (41) and decreased in manic subjects (42). Improvement in mania with lithium and valproate is linked with normalization of pupillary responses (42).

In addition, a recent positron emission tomography (PET) imaging study reported reduced muscarinic type 2 receptor binding in anterior cingulate cortex in subjects with BPD (43). Further supporting the importance of the role of the cholinergic system in BPD was 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 (44,45). 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 six of 11 patients with treatment-resistant mania (46). However, a recent six-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 (47). 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 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 colleagues (48) described the antidepressant properties of the anticholinergic drug biperiden in 10 severely depressed inpatients. More recently, Furey and Drevets (2006) reported on 2 studies that unexpectedly found that the antimuscarinic drug scopolamine had antidepressant properties in both subjects with unipolar and bipolar depression; these effects were rapid, occurring within three to five days (49). In the first of the two studies, four 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 three doses of scopolamine hydrobromide (2.0, 3.0, and 4.0 μg/kg). The second study involved seven sessions where subjects received 15-minute intravenous infusion of a placebo saline solution or scopolamine hydrobromide, 4.0 μg/kg. The number of subjects with BPD was not specified in the first study, but there were nine 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 comparing endpoint with baseline. The authors report 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 (50). In this study, only one patient developed euphoria on scopolamine. Furthermore, no increase in YMRS scores occurred in patients with BPD during scopolamine treatment comparing baseline with study endpoint. In animals, scopolamine has been reported to produce a significant dose-dependent decrease in prepulse inhibition, but had no effect on startle amplitude (51).

Because anticholinergic side effects were 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.

The nicotinic acetylcholine receptor system

The nicotinic acetylcholine receptor (nAChRs) is one of the best characterized neurotransmitter systems. To date, 12 neuronal nAChR subunits have been identified (α 2-10 and β 2-4) (52). The different pentameric nAChR subtypes can result from these subunit combinations and are distinguished based upon 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 α7 homomers, whereas those with high affinity for nicotine have primarily α4 and β2 subunits (53). A link between nicotine and depression has been suggested by epidemiological studies of smokers (54). In animals, nicotine has been reported to have mood elevating properties (hedonic), and its withdrawal induces an anhedonic state (55). Indirect evidence for the involvement of nAChRs in depression was provided by the Flinders Sensitive Line (FSL), a genetic animal model of depression in rats that could be reversed by nicotine treatment (56). Similarly, nicotine has been found to have antidepressant-like properties in a learned helplessness test in rats (57). Cytisine, a partial agonist of high-affinity nAChRs (partial agonist of α4/β2 and a full agonist at α3/β4) was recently found to have antidepressant-like properties in male C57BL/6J mice (58).

Evidence for the involvement of the nicotinic system in BPD includes that mRNA levels of α7 (located at chromosome 15a13-14) and α7-like genes from 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 (59).

In a recent four-week, double-blind study, 11 nonsmokers with depressive symptoms (Center for Epidemiological Studies Depression Scale (CES-D) ≥10) were randomized to either transdermal nicotine (3.5-7.0 mg/day) or placebo. Nicotine induced significant antidepressant

effects when compared to placebo at day eight but not on days 21 or 28. Reported side effects were infrequent and minimal (60). 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 (e.g., 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, a selective α4/β2 nAChR agonist, a subtype-selective ligand high affinity nAChRs was found to have antidepressant-like properties in the learned helplessness model of depression in rats (61). As with fluoxetine and imipramine, a dose-dependent study of subchronic treatment with SIB-1508Y reversed the escape deficit in the learned helplessness model, an effect that was still apparent one week later.

In terms of nicotinic antagonists, a previous study found that comorbid BPD was improved in two 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 two patients; manic symptoms only became apparent upon cessation of mecamylamine treatment (63). Furthermore, a more recent study also found mecamylamine to have antidepressant and mood stabilizing properties (64). In this eight-week, double-blind, placebo-controlled trial, mecamylamine (2.5 to 7.5 mg/day) significantly decreased sudden mood changes in children and adolescents (ages 8 to 17 years) 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 above reports (including small sample size, overlapping comorbid diagnoses, not testing it directly 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 both attenuates ephedrine-induced (65) and quinpirole-induced hyperactivity in rats (66).

In addition, mecamylamine was found in a doseresponse 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 properties (61). Similarly to the opiate agonists, the potential for abuse and/or withdrawals symptoms from these types of compounds needs further study.

The melatonin and serotonin (5-HT2C 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 non-affected offspring of probands with BPD, and in monozygotic twins discordant for BPD (67-69). However, Nurnberger and colleagues did not confirm that melatonin suppression by light occurred in euthymic bipolar patients (70). Thompson and colleagues (71) found a significant association of the Δ502-505polymorphism in GPR50 (also

known as H9, melatonin-related receptor or ML1X, located on Xq28) and susceptibility to BPD in a population from the Southeast of Scotland. However, this finding was not replicated in a Northern Swedish association sample (72).

Interestingly, low doses of both lithium and valproate have been reported to reduce melatonin light sensitivity but not its overall synthesis in healthy volunteers (73,74). There are no controlled studies with melatonin in patients with BPD. Case reports and series indicate mixed results (75,76).

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-HT2C antagonist; the latter property has also been implicated in the mechanism of action of atypical antipsychotic drugs with thymoleptic properties (77). *In vivo* studies indicate that agomelatine increases both norepinephrine and dopamine in frontal cortex. In addition to increasing these neurotransmitters, chronic agomelatine treatment (three weeks) resulted in increased cell proliferation and neurogenesis in the ventral dentate gyrus, as well as increased survival of these newly formed cells (78). Furthermore, similar to lithium (79), agomelatine is able to resynchronize a disrupted circadian rhythm and has circadian phase-advancement properties (80,81). Agomelatine is effective in animal models of depression (specifically, in the FST, chronic mild stress test, and learned helplessness model) (82,83) and anxiety (social interaction test and the Vogel conflict test) (84).

In three large, multi-center, multi-national, placebo-controlled, short-term studies in major depression, agomelatine was found to be a clinically effective and well-tolerated antidepressant (85-87). In the study by Loo and colleagues (85), some patients met criteria for bipolar II disorder [depressed]; 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 (88). Agomelatine also shows a low liability for hypomania or mania in the several studies conducted to date (89), 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 HAM-D17 score of ≥18 were studied. All patients received 25 mg/day of agomelatine for six 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 patient 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 (six weeks), although 6 patients experienced serious adverse events during the one-year period. Three lithium-treated patients experienced manic or hypomanic episodes during the optional extension period, one of which was treatment-related (90). One interesting characteristic of the drug is that it appears that its abrupt cessation does not result in discontinuation symptoms (91).

The 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 the glutamate in the pathophysiology of depression or mechanism of action has been summarized elsewhere (115-117). 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 (118-121). 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 have either been or are now undergoing testing in "proof-of-concept" studies in patients with severe mood disorders (115,117). The glutamatergic modulators that are being developed target either the glutamate receptors (N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (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 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.

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 (ALS). 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 GluR1 and Glur2 (122), and glutamate reuptake (115,122,123). Riluzole is also known to stimulate the synthesis of growth factors, including brain derived neurotrophic factor (BDNF) in cultured mouse astrocytes (124), and was recently shown to have antidepressant-like properties in animal models (Gerard Sanacora, personal communication).

Several clinical studies have been conducted with riluzole. It was found to have antidepressant effects in patients with unipolar depression (125), (126) as well as bipolar depression (127). Overall, riluzole was well tolerated in these trials. 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- but not MK-801-induced hyperlocomotion (128). This characteristic suggests that it might have "antimanic-like" properties but more studies are needed to confirm this.

Ionotropic glutamate receptors

Three subgroups of glutamatergic ion channels have been identified based on 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 in (115)). NMDA receptor antagonists (e.g., MK-801 and AP-7) 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 brain of rats (reviewed in (115,129). 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 of apomorphine (130) and to decrease aggressiveness in the resident-intruder test (131). In humans, D-cycloserine is currently being tested in bipolar depression in a trial supported by the Theodore & Vada Stanley Foundation. A recent study found it to be ineffective in treatment-resistant depression (132). However, in addition to the limitations of this study as acknowledged by the authors (e.g., unevenness in treatment-resistance criteria, concomitant medications, etc), it is notable that in animal studies, a single dose of D-cycloserine elicited dose-dependent reduction in immobility in the Porsolt swim test, whereas multiple doses did not (133). 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 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 (134,135). Memantine is a fairly selective NMDA receptor antagonist at doses of 5-20 mg/day with negligible affinity for other receptors that have been implicated in antidepressant action.

Memantine has antidepressant-like effects when used alone (136) or synergistically with imipramine (137) 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 antianxiety effects in a double-blind, placebo-controlled trial in patients with major depression (138). Although no significant antidepressant effects were found with in this study, it does not disprove the possibility that higher doses of memantine, augmentation strategies, or its use in different populations (e.g., in BPD) may result in positive effects.

A recent open-label study involving eight patients with major depressive disorder suggests that higher doses of memantine might be beneficial for some (139). In addition, a recent case series involving two patients indicated that memantine at doses of 10-20 mg/day improved depressive symptoms and cognitive performance in patients with BPD when added to existing mood stabilizer therapy (140). Another small, open-label trial found that memantine had beneficial effects in hyperactivity and irritability in children with pervasive development disorders; these symptoms often seen in patients with BPD (141). 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 (142). 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 (143).

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 (144,145). The effects noted in the latter study were rapid (within two hours), robust, and relatively sustained (lasting approximately one 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 the 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 its 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 (e.g., AMPA and glutamate (see (146,147) for review). Positive modulators of these receptors—the AMPAkines—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 in (148). Chronic treatment with traditional antidepressants increases the expression of AMPA receptors in hippocampal membranes (149) and the phosphorylation of AMPA receptor subunits (150).

LY392098, an ARP, was found to have “antidepressant-like” properties in the FST and in the tail suspension test. LY392098 alone dose-dependently reduces immobility in a manner similar to classic antidepressants, and at sub-threshold doses it potentiated the antidepressant effects of conventional antidepressants (151). In contrast to conventional antidepressants, this group of compounds does not affect the extracellular concentration of monoamines (152). In primary neuronal cultures, LY392098 increased BDNF mRNA (153), which has been implicated in the mechanism of action of many currently available antidepressants (154,155). Another ARP that is being investigated in depression is S18986, which has also been reported to increase BDNF expression (156,157).

In terms of the effects of standard treatments for BPD (i.e., 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. By contrast, the predominantly antimanic agents lithium and valproate significantly reduced surface expression of GluR1 and GluR2 (122,158). 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.

Because AMPA potentiators appear to have antidepressant-like properties (see above), it is possible that AMPA receptor antagonists could have antimanic effects. The first selective AMPA receptors antagonists to be identified were quinoxalinedone derivatives such as NBQX

(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 (e.g., GYKI 52466) block AMPA receptors via an allosteric site on the receptor-channel complex (159). 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 in (160)).

NS1209 ([8-methyl-5-(4-(N,N-dimethylsulfamoyl)phenyl)-6,7,8,9.-tetrahydro-1H-pyrrolo [3,2-h]-iso-quinoline2,3-dione-3-O-(4-hyroxybutyric acid-2yl)oxie]; SPD502) is a structurally novel, water-soluble, competitive AMPA receptor antagonist with good central nervous system bioavailability (161). NS1209 has been well-tolerated in Phase I/II clinical trials and is being evaluated for the treatment of refractory status epilepticus (reviewed in (160).

Metabotropic Glutamate Receptors (mGluRs)

The mGluRs comprise a family of eight receptor subtypes (mGluR1-GluR8), which are classified into three 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 phospholipase C signal transduction pathway. Group II (mGluR2 and mGluR3) and III (mGluR4 and mGluR6-mGluR8) receptors are both coupled in an inhibitory manner to the adenylyl cyclase signal transduction pathway, generally involved in the regulation of release of glutamate or other neurotransmitters (e.g., GABA) depending on synaptic localization (162). The mGluRs are involved in the early phase of memory formation and the mechanism of long-term depression (163-165). The Group I mGluR5 antagonists MPEP (2-methyl-6-[phenylethynyl]-pyridine) and MTEP ([(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine) have shown antidepressant-like activity in the modified FST in rats (166), tail suspension test in mice (166), and olfactory bulbectomized rats (167). Furthermore, MPEP treatment was recently found to increase hippocampal mRNA level (168). The mGluR1 antagonist EMQMCM ([3-ethyl-2-methyl-quinolin-6-yl]-(4-methyoxy-cyclohexyl)-methanone methanesulfonate) was active in the modified FST in rats and in the tail suspension test in mice (169).

The mode of antidepressant-like activity of mGluR1 or -5 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 (see above). 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 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 (170). More recently, the mGluR5 positive allosteric modulator 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) was found to be brain penetrant and to reverse amphetamine-induced locomotor activity and amphetamine-induced deficits in prepulse inhibition in rats, two models thought to be sensitive to antipsychotic treatment (171). 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 are published on whether it has an antidepressant profile.

Group II mGluR2, 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 post-synaptic mechanisms. Group II mGluRs agonists (e.g., 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 (172). Moreover, MGS-0039 has been reported to be effective in the learned helplessness model of depression (173) and to increase cell proliferation in the adult mouse hippocampus (174). 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 NBQX blocked the antidepressant-like activity of MGS-0039 in the tail suspension test in mice (175).

A type 2 mGluR receptor agonist, LY 354740, was recently tested in patients with panic disorder. LY 354740 failed to separate from placebo in the primary panic measures, whereas paroxetine did. Although the MADRS scale was collected at baseline and at week nine, no MADRS score was reported for these time points. The compound was generally well-tolerated; the most common 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 (176). A multi-center trial of LY35470 for the treatment of panic disorder was suspended because preclinical studies showed convulsions in mice (177). No noticeable antipsychotic effects were noted with LY 35470, as indicated by its inability to block the increase in PANSS scores due to ketamine infusion (178). Unfortunately, no information is available in depression paradigms.

Pilc and colleagues demonstrated that a selective group III mGluR agonist (ACPT-I, [1S,3R, 4S]-1-aminocyclo-pentane-1,3,4-tricarboxylic acid) and a mGluR8 agonist (RS-PPG, [RS]-4-phosphonophenylglycine) for this receptor resulted in antidepressant-like effects in the FST in rats (179). Additional proof for the involvement of group II mGluRs comes from the work of Cryan and colleagues, who have shown that mGluR7 knockout in mice produces antidepressant-like effects in the FST and in the tail suspension test in mice (180). Palucha and colleagues similarly reported the antidepressant-like effects of group III mGluR agonists in the behavioral despair test (181).

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.

The Hypothalamic-Pituitary Adrenal (HPA) Axis

Dysfunction of the hypothalamic-pituitary adrenal (HPA) axis has been well-described in bipolar depression. Hypercortisolemia may be central to the etiopathogenesis of both 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 and ketoconazole) (182), hydrocortisone, dexamethasone (183,184), and dehydroepiandrosterone (DHEA) (reviewed in (185). Treatment with glucocorticoid synthesis inhibitors (e.g., ketoconazole and metyrapone), the CRF1 receptor antagonist R-121919, and DHEA have been observed to ameliorate depressive symptoms in patients with unipolar depression (reviewed in (185-188). Clinical development of R-121919 was terminated because of its association with abnormal liver function tests (189). DHEA has also been reported to be associated with a high propensity to induce mania (190).

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 six depressed patients who had a diagnosis of treatment-resistant BPD (191). 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 one placebo-controlled study of an antiglucocorticoid for bipolar depression has been performed. Mifepristone (RU-486) is a non-selective antagonist of the glucocorticoid receptor that has been reported to have antidepressant and antipsychotic properties in patients with psychotic depression (182) reviewed in (185), although a recent letter to the editor indicates that two large Phase III studies failed to find significant antipsychotic or antidepressant effects (192). 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 colleagues (2004) compared mifepristone (600 mg) to placebo in 20 subjects with bipolar depression (193). Over the course of the six-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 (194). In addition, mifepristone has significant anti-progesterone effects, and its chronic use could lead to fatigue, hot flashes, and gynecomastia/breast tenderness, and endometrial hyperplasia (195). 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.

CRF1 receptor antagonists—A number of small molecule CRF 1R antagonists have been evaluated using *in vivo* paradigms in animal models to attenuate CRF-induced adrenocorticotropic hormone (ACTH) release (196). Several classes of CRF 1R inhibitors have been identified (Table 1) (see (196,197) for review). In preclinical studies, CRF 1 antagonists diminished CRF-induced ACTH release as well as CRF-induced cAMP production (see (196) for review). In an open-label study, R-121919 reduced anxiety and depressive symptoms in patients with major depression (187). Some companies have discontinued clinical development of these compounds because of laboratory abnormalities. Recently, however, an extended data report of a clinical study in major depression patients found no serious side effects or clinically significant abnormal laboratory parameters (including liver enzymes); as a result, development of CRF 1R antagonists for depression continues (198).

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 stress-induced inhibition of exploratory and sexual behaviors (199). Using 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 compared to stressed, untreated animals (200). Antalarmin reduced swim-stress-induced ACTH response but did not show antidepressant-like effects in the FST (201).

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 (202), and shows antidepressant-like properties in the learned

helplessness model of depression in rats (203). 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 (204). In addition, SSR125543A was able to reverse stress-induced suppression of neurogenesis in mice subjected to chronic mild stress (205), and it has also been shown to reduce aggressive behaviors in male Syrian hamsters in the resident intruder aggression test (206). In other studies, CRA 1000, a non-peptide pyrimidine CRF 1 antagonist, was found to reduce immobility in the learned helplessness paradigm in male Wistar rats (207). 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 (208).

Glycogen synthase kinase-3 (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 (e.g., the Wnt pathway, PI3 kinase pathway, protein kinase A, protein kinase C).

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 pro-apoptotic, while 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 (92)).

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, believed to represent —albeit imperfectly—an animal model of mania (93). Furthermore, mice overexpressing a constitutively active form of GSK-3β in the brain showed increased locomotor activity, as well as decreased habituation in an open field. Supporting 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 (94,95). Thus, decreased expression of GSK-3β resulted in attenuation of stimulant-induced locomotion, while 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).

Protein kinase C (PKC) signaling cascade

PKC is highly enriched, has a heterogeneous distribution in 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 (96-101). These findings provide ample evidence that the PKC signaling pathway is clearly a target for the actions of two structurally highly dissimilar antimanic agents—lithium and valproate—and provide the impetus to test a PKC inhibitor in mania. While 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 mice (102), but does reduce amphetamine-induced hyperactivity in a large open field and amphetamine-induced phosphorylation of GAP-43 (103).

In humans, tamoxifen was found to have significant antimanic effects. In a single-blind study, tamoxifen treatment significantly decreased manic symptoms in five of seven patients enrolled in the initial trial. In another recently completed double-blind, placebo-controlled trial with tamoxifen in patients with bipolar mania, tamoxifen exhibited significant antimanic effects as early as day five and throughout the three weeks of the trial (104). 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 (105,106). Other drugs with PKC inhibitor 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. Regarding 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 (105), (107). To our knowledge, the PKC line of research provides evidence for the first time in BPD drug development of a direct molecular target where its 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.

The arachidonic acid cascade

Accumulating data suggest that an inflammatory process is involved in the pathophysiology of mood disorders. The enzymes that regulate the brain arachidonic acid (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 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 (108). In addition, lithium down-regulates the gene expression and protein levels of an AA-specific phospholipase, A2 (cPLA2), as well as the protein levels of COX-2. Valproate decreases turnover of AA, protein levels of COX-1 and COX-2 (109), and frontal cortex COX-2 mRNA (110). 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 (111). In humans, celecoxib was also found to have

antidepressant properties. In a six-week, double-blind, placebo-controlled trial, Muller and colleagues found that celecoxib (400 mg/day) when added to reboxetine in patients with major (unipolar) depression, produced significant antidepressant effects compared to placebo (112). Recently, a six-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 one, not at study endpoint (113). Notably, it remains unclear how brain penetrant celecoxib actually is. In addition, it is also presently unclear whether directly targeting COX-2 is a worthwhile, because selective COX-2 inhibitors may be associated with an increased risk of adverse cardiovascular outcomes (114).

Bcl-2 enhancers

As discussed above, 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 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 expression (209); 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, which 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 CNS function. Thus, mounting evidence suggests that mitochondrial Ca^{2+} 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 may be due to its ability to robustly upregulate Bcl-2. It is also noteworthy that pramipexole similarly upregulates Bcl-2 in several brain areas (210), and has been shown to exert antidepressant effects in two small, double-blind placebo-controlled trials in patients with bipolar depression (211), (212). Future studies would have to test whether selective Bcl-2 enhancers without dopamine effects also have antidepressant effects in bipolar depression.

Other drugs being tested in BPD

Modafinil is approved as a wake-promoting agent for the treatment of excessive daytime sleepiness in narcoleptic patients (213). 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, the dopaminergic and noradrenergic systems. More specifically, it is known to activate noradrenergic α1 receptors, to increase phosphorylation of mitogen-activated protein kinase (MAPK) 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 (214), to increase 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 six-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 vs. placebo and from week two on between the groups (215). No manic switches were reported. In another study, Frye and colleagues (unpublished, reported in (216)) compared the adjunctive use of modafinil (100 or 200 mg in the morning for three 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 baseline to endpoint change on the Inventory for Depressive Symptoms (IDS), percentage response rate, remission rate, and clinical global impression (CGI) improvement. Modafinil was not significantly associated with a treatment-emergent manic episode. One case report described a manic switch in a patients with treatment-resistant bipolar depression treated with modafinil (217), and two cases of modafinil-induced irritability and aggression in two bipolar patients have been described (218).

A proprietary formulation of the nucleoside uridine—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. A previous study suggested that RG2133, the prodrug of RG2419, had antidepressant-like effects in an animal model of depression. In a six-week Phase 1 clinical trial involving 19 patients with major depression or bipolar depression, RG2133 was found to be safe, did not induce mania, and provided early evidence of a clinical effect. These data have not been published but are available online at http://www.medicalnewstoday.com/medicalnews.php?newsid=39227. RG2417 was recently found to be efficacious in a Phase 2a multi-site study in bipolar depression. This was a multi-center study in which 84 patients received either RG2417 or a placebo twice a day. Over the six-week treatment period, patients receiving RG2417 demonstrated a statistically significant improvement in the symptoms of depression when compared to those patients receiving placebo on the MADRS ($p=0.03$) and a strong trend toward 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; 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 multi-site study (study ID# 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-HT2C receptor) system, (5) the glutamatergic system, and (6) the HPA axis as well as the (7) GSK-3 protein, (8) PKC, (9) the arachidonic acid cascade, and (10) other systems.

Drug development for BPD may occur through one of two approaches (117): the first is by understanding the therapeutically relevant biochemical targets of currently effective medications; examples of this approach were reviewed here and include the common targets of lithium and valproate, which are PKC and GSK-3β. The investigation of PKC illustrates how this approach could lead to 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: 1) the drugs/drug mechanisms reviewed here are potentially worthy of study in one 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; 2) 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; and 3) when deciding on a drug mechanism or target to pursue in drug development for BPD, consideration should be giving to 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/developed primarily on the presumptive drug mechanism alone (reviewed in (219)).

Enriched criteria for establishing target validation for further development in BPD have been proposed (97,154). 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 (220).

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Table 1
Examples of Candidate Drugs for the Treatment of BPD

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); Donepezil (cholinesterase inhibitor)
Nicotinic acetylcholine receptor	Cytisine (partial agonist of α4/β2 and a full agonist at α3/β4); SIB-1508Y (α4/β2 agonist); mecamylamine (nicotinic antagonist)
Melatonin and serotonin system	Agomelatine (melatonin MT1 and MT2 agonist and 5HT2C antagonist)
GSK	GSK inhibitors: Zinc, indirubines, maleimides, hymenialdesine, paullones, thiaziazolidones, synthetic phosphorylated peptide, azole derivatives
PKC	PKC inhibitors: tamoxifen, LY33531, ruboxistaurin, rottlerin, indolocarbazoles, UCN-01, CGP41251, PKC412, bisindolylmaleimides, balanol, indolylindazolylmaleimides, 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, ketamine
AMPA receptor potentiators	Benzoylpiperidone (aniracetam), benzoylpyrrolidines (ampakines), arylpropylsulfonames (LY392098, LY451616), S18986
mGluR	MPEP, MTEP, EMQMCM, CDPPB (Group I mGlu R5 antagonists); LY341495, MGS-0039 (Group II mGluR2s); GluR2/3 agonists; ACPT-I and RS-PPG (III mGluR agonists)
Glucocorticoid synthesis	Glucocorticoid synthesis inhibitors: ketoconazole, aminogluthethimide, metyrapone
GR II receptor	GR II receptor antagonists: mifepristone (RU-486), ORG 34517, ORG 34850, ORG 34116, AL082D06, cyproterone acetate
CRF 1 receptors	CRF 1R antagonists: peptides (astressin, α-helCRF), small molecule non-peptides (CP-154526, antalarmin, DMP-695, DMP-696, CRA-1000, R-121919, SSR-125543, NBI 35965, NBI 27914)
Bcl-2 enhancer	Pramipexole

*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 those are due to valproate's ability to inhibit GSK-3 and HDAC.

Abbreviations: **AMPA**, α-amino-5-methyl-3-hydroxy-4-isoxazole propionic acid; **Bcl-2**, B cell lymphoma-2; **CRF**, corticotrophin releasing factor; **GC**, glucocorticoids; **DHEA**, dihydroepiandrosterone; **GR**, glucocorticoid receptor; **GSK**, glycogen synthase kinase; **HDAC**, histone deacetylase; **mGluR**, metabotropic glutamate receptors; **NMDA**, N-methyl-D-aspartate receptor; **PKC**, protein kinase C.

[NB: DHEA IS NOT IN THE TABLE; GC IS NOT IN THE TABLE]