

Review of Pharmacological Treatment in Mood Disorders and Future Directions for Drug Development

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After a series of serendipitous discoveries of pharmacological treatments for mania and depression several decades ago, relatively little progress has been made for novel hypothesis-driven drug development in mood disorders. Multifactorial etiologies of, and lack of a full understanding of, the core neurobiology of these conditions clearly have contributed to these development challenges. There are, however, relatively novel targets that have raised opportunities for progress in the field, such as glutamate and cholinergic receptor modulators, circadian regulators, and enzyme inhibitors, for alternative treatment. This review will discuss these promising new treatments in mood disorders, the underlying mechanisms of action, and critical issues of their clinical application. For these new treatments to be successful in clinical practice, it is also important to design innovative clinical trials that identify the specific actions of new drugs, and, ideally, to develop biomarkers for monitoring individualized treatment response. It is predicted that future drug development will identify new agents targeting the molecular mechanisms involved in the pathophysiology of mood disorders.

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INTRODUCTION

The major mood disorders—bipolar disorder (acute mania and bipolar depression) and major depressive disorder—represent a spectrum of brain disorders with multiple etiologies, including genetic vulnerability, environmental stress, dysregulation of neurotransmission, abnormal neuroplasticity, and altered gene expression (Chen *et al*, 2010; Krishnan and Nestler, 2010; Pittenger and Duman, 2008). However, currently available pharmacological agents for mood disorders were often discovered serendipitously, with the mechanisms of action only partially understood after the initial demonstration of clinical effects. In the sections below, we briefly review the available pharmacological treatment of mood disorders and their proposed mechanisms of action. Obviously, future drug development needs

to have a greater understanding of mechanisms with hypothesis-driven clinical trials based on preclinical findings. Recent treatment development has already moved toward this direction, although gaps remain between preclinical findings and clinical trial outcomes. In this review, we primarily summarize those newly developed treatments with some supportive data at the level of clinical trials. Finally, we will discuss outstanding issues that need to be considered for treatment development in mood disorders.

Anti-manic and Mood-Stabilizing Medications

Lithium was the first psychotropic with a specific indication for bipolar disorder. Its efficacy in acute mania (Cade, 1949), especially mania with typical clinical features (ie, euphoric mood, grandiosity), has been confirmed in many clinical trials (Goodwin and Jamison, 2007). Anti-manic efficacy tends to be reduced in mixed states, rapid cycling, multiple prior episodes, or comorbid substance use disorders. As a small ion, lithium freely penetrates into neurons and is likely to interact with multiple intracellular molecules. The precise mechanism of therapeutic action

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of lithium remains to be elusive, but the candidate cellular targets of lithium appear to be enzymes such as inositol phosphatases (Berridge *et al*, 1982) and glycogen synthase kinase-3 (GSK3) (Klein and Melton, 1996) (Figure 1).

The introduction of antiepileptics as a treatment option for bipolar disorder resulted, in part, from preclinical models of limbic kindling, and behavioral sensitization resembled the longitudinal course of illness progression in bipolar disorder (Goddard, 1967). Early proof-of-concept studies (Okuma *et al*, 1979, 1981; Post, 1990a, b; Post *et al*, 1982) and subsequent clinical trials have led to two FDA-approved antiepileptics for treatment of acute mania, divalproex sodium (Bowden *et al*, 2000; Freeman *et al*,

1992; Pope *et al*, 1991) and extended-release carbamazepine (Weisler *et al*, 2005). Both are effective in euphoric mania, like lithium, but also mixed mania where lithium appears to be somewhat less effective. Despite a different medication class, valproic acid and carbamazepine may directly or indirectly affect similar signaling mechanisms targeted by lithium (Gurvich and Klein, 2002). Lithium, valproic acid, and carbamazepine have common effects on the depletion of the phosphoinositide precursor inositol (Williams *et al*, 2002). All three drugs also reduce brain arachidonic acid, although by targeting different lipid metabolic processes (Rao *et al*, 2008). However, the significance of these common cellular effects in their anti-manic action remains

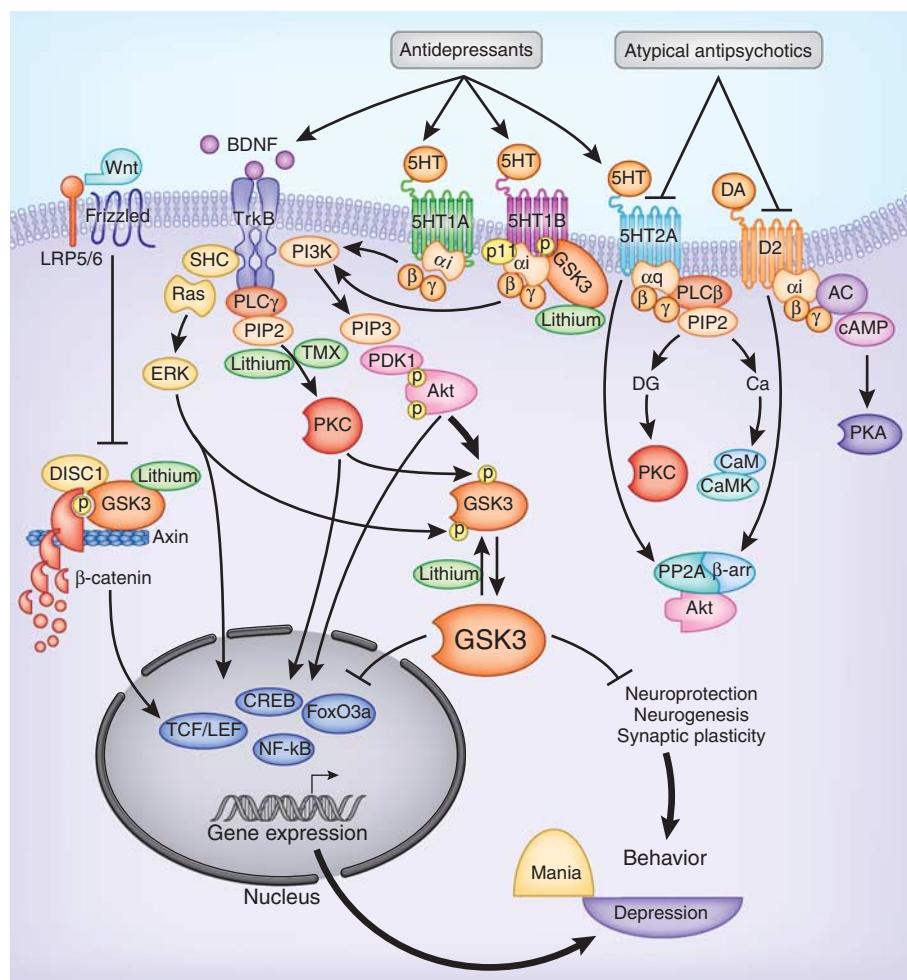


Figure 1. Signal transduction pathways mediating the actions of lithium and monoamine-regulating drugs. Lithium directly inhibits GSK3 and facilitates the phosphorylation of GSK3 at the N-terminal serine. Lithium also inhibits inositol phosphatases to block phosphatidylinositol signaling. Antidepressants facilitate serotonin action on serotonin receptors as well as facilitate neurotrophic receptor activity. Atypical antipsychotics block both serotonin 2A and dopamine D2 receptors. Activation of these monoamine receptors causes the activation or inhibition of Akt, PKC, or Erk through different signaling pathways. Akt and PKC phosphorylate GSK3 at the N-terminal serine and Erk phosphorylates GSK3 at the C-terminal serine, which cause GSK3 inactivation. Tamoxifen inhibits PKC. These signaling cascades directly or indirectly regulate gene expression and neuroplasticity that have an impact in mood regulation. AC, adenylyl cyclase; Ca, calcium; CaM, calmodulin; CaMK, calmodulin-dependent protein kinase; cAMP, cyclic adenosine monophosphate; CREB, cAMP-responsive element-binding protein; DG, diacylglycerol; DISC1, disrupted in schizophrenia-1; ERK, extracellular signal-regulated kinase; FoxO, forkhead 'O' transcription factor; GSK3, glycogen synthase kinase-3; IP3, inositol trisphosphate; LRP5/6, low-density lipoprotein receptor-related protein-5/6; MEK, mitogen-activated protein kinase; NF- κ B, nuclear factor- κ -B; PDK1, phosphoinositide-dependent protein kinase-1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2); PIP3, phosphatidylinositol-(3,4,5)-trisphosphate (PtdIns(3,4,5)P3); PKA, protein kinase-A; PKC, protein kinase-C; PLC, phospholipase-C; PP1, protein phosphatase-1; PP2, protein phosphatase-2, TMX, tamoxifen; TrkB, tyrosine kinase-B; β -arr, β -arrestin.

unknown. Besides their common intracellular actions, valproic acid and carbamazepine block sodium channels to reduce neuron excitability (Figure 2), which is a proposed mechanism for their antiepileptic action (Macdonald and Kelly, 1995). Although it has not acquired regulatory approval, two placebo-controlled clinical trials have shown that phenytoin, another sodium channel blocker, also has an anti-manic and bipolar prophylactic effect as add-on treatment (Mishory *et al*, 2003, 2000). However, not all antiepileptic drugs have noticeable anti-manic effects (Gajwani *et al*, 2005), leaving the direct association of their antiepileptic effects with bipolar disorder inconclusive. Valproic acid also has been reported to inhibit GABA transaminase (Rosenberg, 2007), reduce the synaptosomal α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits GLuR1 and GluR2, and AMPA receptor trafficking (Du *et al*, 2008, 2004) and increase the turnover of vesicular glutamate transporter (Kang *et al*, 2005); these results suggest a role for valproic

acid in modulating glutamate neurotransmission and synaptic plasticity (Figure 2). Valproic acid is also a weak histone deacetylase (HDAC) inhibitor that facilitates histone acetylation and enhances the expression of many genes (Phiel *et al*, 2001). Carbamazepine appears to have certain mechanisms of action distinctive from valproic acid (Eyal *et al*, 2004; Mai *et al*, 2002), which remain to be fully investigated.

Lamotrigine is the only other antiepileptic with clear benefit for bipolar disorder and is approved by FDA for maintenance treatment (Bowden *et al*, 2003; Calabrese *et al*, 2003). Lamotrigine is not an effective anti-manic agent, but the lack of acute effect in mania may be attributable to the slow dosage titration that is required to prevent its serious adverse effects, including Stevens–Johnson syndrome (Schmidt and Kramer, 1994). Lamotrigine has demonstrated efficiency for maintenance mood stabilization, especially for preventing relapse into depression (Calabrese *et al*, 2003). Although only approved by FDA for the maintenance phase

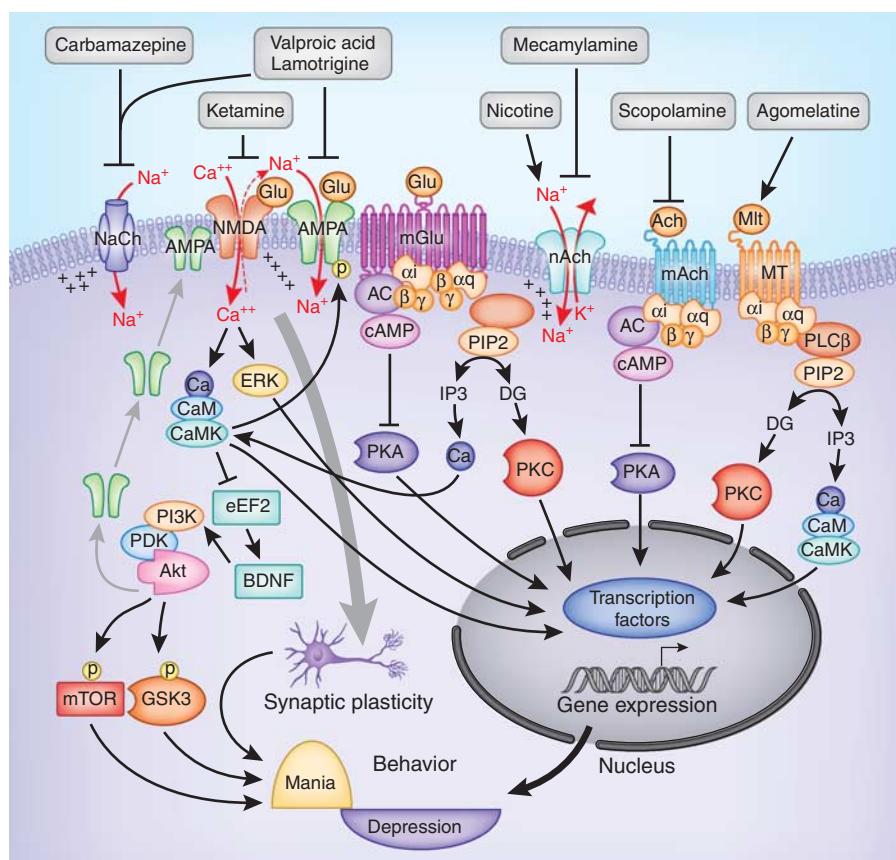


Figure 2. Regulation of intracellular signaling by antiepileptics and modulators of glutamate, acetylcholine, and melatonin systems. The antiepileptic drugs are either sodium channel blockers or have a direct effect on AMPA receptors. Ketamine is an antagonist of NMDA receptors. Activation of ionotropic glutamate receptors increases intracellular sodium and calcium to regulate downstream protein kinases such as CaMK, Akt, and Erk. Blocking NMDA receptors by ketamine can induce the activation of Akt, which activates the mTOR pathway and inhibits GSK3. Ketamine also increases BDNF synthesis induced by elongation factor-2. Nicotine activates and mecamylamine blocks nicotinic acetylcholine receptors; scopolamine is an antagonist of muscarinic receptors; and agomelatine activates melatonin receptors. Metabolic glutamate, muscarinic acetylcholine, and melatonin receptors regulate G-protein-coupled signaling pathways such as PKA, PKC, and CaMK. AMPA, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor; BDNF, brain-derived neurotrophic factor; CaMK, calcium/calmodulin-dependent protein kinase; eEF2, elongation factor-2; mACh, muscarinic acetylcholine receptor; mGlu, metabolic glutamate receptor; MT, melatonin receptor; mTOR, mammalian target of rapamycin; nACh, nicotinic acetylcholine receptor; NaCh, sodium channel; NMDA, *N*-methyl-D-aspartic acid receptor.

of bipolar-I disorder (Bowden *et al*, 2003; Calabrese *et al*, 2003), additional studies (Frye *et al*, 2000; van der Loos *et al*, 2009) and a recent meta-analysis of clinical trials (Geddes *et al*, 2009) have suggested a specific effect of lamotrigine in bipolar depression. Besides blocking sodium channels (Cheung *et al*, 1992; Prica *et al*, 2008; Zona and Avoli, 1997), lamotrigine potently inhibits presynaptic glutamate neurotransmission by direct inhibition of glutamate release (Leach *et al*, 1986). In addition, lamotrigine may also modulate glutamate neurotransmission by increasing the membrane-surface expression of AMPA receptor subunits (Du *et al*, 2007) and inhibition of postsynaptic AMPA receptor-induced currents (Lee *et al*, 2008). More recently, lamotrigine has been found to selectively suppress $\alpha 4\beta 2$ nicotinic acetylcholine receptor-mediated currents in freshly dissociated ventral tegmental dopamine neurons, suggesting that lamotrigine may inhibit nicotinic acetylcholine receptor function in this brain area (Zheng *et al*, 2010). Glutamate and acetylcholine receptor ligands both represent newer targets for antidepressant drug development (see additional discussion later in this review).

Antidepressants

The earliest drugs discovered to be effective for the treatment of depression include monoamine oxidase inhibitors (MAOIs) (Youdim and Bakhle, 2006) and tricyclic antidepressants (TCAs) (Klerman and Cole, 1965). More recent medications, including serotonin-selective reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and a few atypical antidepressants, such as mirtazapine and nefazodone, have improved side-effect profiles but are no more effective than MAOIs and TCAs. All these drugs share similar mechanisms of enhancing or otherwise modulating serotonin and norepinephrine neurotransmission. Therefore, currently available antidepressants largely have a limited set of mechanisms and may contribute partially to inadequate remission rates for major depression found in contemporary clinical trials.

As evidenced by the NIMH-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Rush *et al*, 2006), remission rates with current antidepressant treatment were not robust. The STAR*D study enrolled 3671 patients to four sequential levels of treatment based on non-remission. The findings of the study were striking; only about 1/3 of participants remitted at the first-level treatment with citalopram. There were only modest differences between the individual treatments at each subsequent level; the remission rates for Levels 1–4 were 36.8%, 30.6%, 13.7%, and 13.0%, respectively, indicating diminishing responses across the four levels. Although 67% of the participants remitted, about half relapsed over a 1-year follow-up with increased rates at successive levels of care (40.1%, 55.3%, 64.6%, and 71.1% relapse for Levels 1–4, respectively). This landmark study demonstrated several salient facts on the available antidepressants: (1) Depression is difficult to treat

to remission; (2) sustained remission with any available option or even multiple treatment steps remain unacceptably low and hard to maintain; (3) intolerance rates are unacceptably high; and (4) most notably, modulating monoamine neurotransmission alone is not sufficient for sustained treatment of depression for the majority of patients (Shelton *et al*, 2010).

The impressive lack of response/remission with antidepressants is even more striking in bipolar depression than in major depression (Frye, 2011). In the NIMH-funded 26-week Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (Sachs *et al*, 2007), bipolar depressed patients treated with a mood stabilizer were randomized to adjunctive antidepressant therapy (paroxetine or bupropion) or placebo, but there were no significant differences among groups in the rates of durable recovery, defined as eight consecutive weeks of euthymia without switch to mania/hypomania. A recent randomized trial comparing paroxetine monotherapy and quetiapine in bipolar depression also suggested that paroxetine was less effective in improving depression and was more likely to cause a switch to mania/hypomania (McElroy *et al*, 2010). Finally, a recent meta-analysis of 15 randomized, double-blind trials comparing acute antidepressant with either placebo or active comparator in bipolar-I and II depressed patients demonstrated non-significant benefits of antidepressant therapy over placebo ($p < 0.09$) in rates of remission (Sidor and Macqueen, 2011). In current clinical practice, antidepressant monotherapy is not recommended for bipolar depression, particularly bipolar-I, owing to the concern of its mania-inducing effect (Frye *et al*, 2009). In fact, bipolar depression has been an exclusion criterion in most antidepressant clinical trials, which may have contributed to the unsure efficacy of any new antidepressant in the treatment of bipolar depression. The general non-responsiveness of bipolar depression to the available monoamine-modulating antidepressant treatment and the risk of inducing mania suggest that the neuropathology of bipolar depression likely involves mechanisms beyond monoamine neurotransmission, which need to be identified to develop effective treatment.

Antipsychotics in Mood Disorders

Conventional antipsychotics block dopamine D2 receptors and have acute anti-manic and anti-psychotic effects in acutely ill bipolar patients (Tohen and Vieta, 2009). Among them, chlorpromazine is the only one that has FDA indication for treatment of bipolar mania. Most atypical antipsychotics available in the United States, except for clozapine, paliperidone, iloperidone, and lurasidone, have received FDA approval for bipolar mania.

Some atypical antipsychotics, either as monotherapy or augmentation, have also shown efficacy in ameliorating symptoms of bipolar depression and treatment-resistant major depression. Quetiapine has demonstrated efficacy in bipolar depression (Calabrese *et al*, 2005) and has received

FDA indication as monotherapy for this condition. Olanzapine plus fluoxetine is an FDA-approved combination treatment for bipolar depression (Tohen *et al*, 2003). Aripiprazole and quetiapine have shown antidepressant efficacy as augmentation treatment to antidepressant in major depressive disorder (Bauer *et al*, 2009; Berman *et al*, 2007; Marcus *et al*, 2008) and have recently received FDA approval for this indication.

The mechanisms of atypical antipsychotics in the treatment of mood disorders remain unclear. These agents not only are antagonists of dopamine D2 receptors (as with the typical antipsychotics), but also block type-2 serotonin (5-HT2) receptors, particularly 5-HT2A and 5-HT2C receptors (Markowitz *et al*, 1999; Meltzer *et al*, 1989). Blockade of 5-HT2A receptors is a mechanism of action of certain antidepressants, particularly trazodone and nefazodone. The contribution of 5-HT2A/2C blockade to the antidepressant actions of atypical antipsychotics is unclear, but may involve their effect on forebrain norepinephrine and dopamine neurotransmission (Zhang *et al*, 2000). Additionally, aripiprazole, ziprasidone, and asenapine are 5-HT1A receptor partial agonists, which have also been shown to enhance the release of norepinphrine and dopamine (Ghanbari *et al*, 2009; Gobert *et al*, 1999; Hajos-Korcsok *et al*, 1999). Although the exact mechanism remains elusive, the apparent superior efficacy of these drugs to conventional antipsychotics as mood-stabilizing agents suggests that this effect occurs through actions beyond a D2 receptor antagonistic action (Blier and Szabo, 2005) (Figure 1).

In summary, a group of anti-manic agents have been effectively used to control acute mania, and the efficacy of those clinically used anti-manic treatments are supported by meta-analysis of available clinical data (Yildiz *et al*, 2011). Evidently, current treatment of depression for both major depressive disorder and bipolar depression is limited, and the efficacy of treatment is not satisfactory. This problem may be attributable to the focus in antidepressant development to date primarily on the monoamine-modulating mechanism of action. Therefore, new treatments for depression are needed, particularly antidepressants that have new mechanisms of action and target a broader set of depressive symptomatology. In the next few sections, we will review pharmacological treatments that have promising efficacy in depression or mania, and discuss issues in concern when they are advanced to clinical implications.

NEW TREATMENT DEVELOPMENT IN MOOD DISORDERS

Improved Treatment Targeting Monoamine Neurotransmission

For decades, monoamine-regulating drugs are the only class of antidepressants available; thus, there is no doubt that balanced monoamine neurotransmission is important in mood regulation. However, the majority of these drugs,

including MAOIs, TCAs, SSRIs, SNRIs, and the α 2-adrenergic antagonist, mirtazapine, globally alter the synaptic neurotransmission of serotonin and/or norepinephrine, and are non-selective to each type of serotonin and norepinephrine receptors. At least 13 subtypes of serotonin receptors and five subtypes of noradrenergic receptors have been identified. These monoamine receptors have different and specific functions in defined brain regions. Therefore, unless the role of each of these receptors in mood regulation is fully characterized, the most effective treatment of depression by targeting monoamine neurotransmission may not be developed.

5-HT1A receptors have been studied extensively for their roles in regulating mood and anxiety in both animal and human studies (Akimova *et al*, 2009; Leonardo and Hen, 2008; Parks *et al*, 1998; Polter and Li, 2010b; Price and Drevets, 2010; Ramboz *et al*, 1998; Savitz *et al*, 2009). However, trials of 5-HT1A receptor full or partial agonists for depression have been unsuccessful, with only buspirone, a 5-HT1A receptor partial agonist, receiving FDA approval as an anxiolytic agent (Goldberg, 1979; Goldberg and Finnerty, 1979). In fact, the delayed onset of serotonin reuptake inhibitor antidepressants is thought to be partly due to the time required to desensitize the presynaptic 5-HT1A autoreceptors (Albert and Lemonde, 2004; Blier and Ward, 2003; Martin *et al*, 1990, 1991) that express in the serotonin neurons (Bockaert *et al*, 2006) and negatively regulate serotonin release (Sprouse and Aghajanian, 1987). Thus, blockade of 5-HT1A receptors may accelerate response to SSRIs (Arborelius, 1999) instead of enhancing the overall responsiveness to antidepressants (Shelton *et al*, 2010).

Although remaining to be thoroughly investigated, 5-HT1B and 5-HT4 receptors are potential targets for new antidepressants (Lucas, 2009; Ruf and Bhagwagar, 2009), particularly with evidence showing their intimate association (Svenningsson *et al*, 2006; Warner-Schmidt *et al*, 2009) and brain colocalization (Egeland *et al*, 2011) with a small adaptor protein p11 (Donato, 1999; Marenholz *et al*, 2004). Expression of p11 is decreased in the cingulate cortex in animal models of depression (Svenningsson *et al*, 2006) and in postmortem brains of depressed suicide subjects (Anisman *et al*, 2008). Additionally, mice with neuron-targeted deletion of p11 show a depressive phenotype (Svenningsson *et al*, 2006). Conversely, upregulation of p11 expression can be induced by antidepressant treatment, electroconvulsive therapy, and brain-derived neurotrophic factor (BDNF) (Svenningsson *et al*, 2006; Warner-Schmidt *et al*, 2010), and behaviors of transgenic mice with p11 overexpression mimic the effects of antidepressants (Svenningsson *et al*, 2006). The association of p11 with 5-HT1B and 5-HT4 receptors causes an increase in the cell-surface expression of these receptors (Svenningsson *et al*, 2006; Warner-Schmidt *et al*, 2009), raising the possibility that the behavioral effect of p11 is mediated by enhancing serotonin-regulated neuron activity through these receptor subtypes (Svenningsson and Greengard, 2007).

Noticeably, functions of 5-HT1B receptors are complex owing to its autoreceptor and heteroreceptor expression in different types of neurons (McDevitt *et al*, 2011; Sari, 2004), but agents targeting specific subtypes of 5-HT1B receptors are not yet available. Interestingly, in several earlier studies, 5-HT1B receptor activity and associated behaviors were found to be regulated by the mood stabilizer lithium (Januel *et al*, 2002; Massot *et al*, 1999; Redrobe and Bourin, 1999), which appeared to be a selective effect to 5-HT1B receptors, as lithium did not elicit similar regulation on 5-HT1A receptors (Redrobe and Bourin, 1999). From various molecular approaches, it is now clear that the selective effect of lithium on 5-HT1B receptors is likely the result of inhibition of an intracellular protein kinase, GSK3 (Figure 1), as GSK3 selectively interacts and differentially facilitates 5-HT1B receptor-regulated G-protein signaling, serotonin release, and associated behaviors (Chen *et al*, 2009, 2011). As discussed in more detail later in this review, GSK3 has been increasingly recognized as a protein kinase involved in mood regulation, and it is a potential therapeutic target of several classes of drugs used in the treatment of mood disorders (Li and Jope, 2010b). Therefore, 5-HT1B receptors act as an anchor of serotonin signaling to mood regulation through interaction with p11 and GSK3. This unique characteristic of 5-HT1B receptors calls for developing agents that facilitate p11 or disrupt GSK3 interaction with 5-HT1B receptors, as these specific protein interactions may modify 5-HT1BR function for the treatment of depression.

5-HT4 receptor-selective agonists have been tested in preclinical animal models for their antidepressant effect. In several tests measuring mood-related behaviors, the 5-HT(4) agonist RS67333 was found to elicit a strong antidepressant-like action and the effect is accompanied by rapid induction of 5-HT1A receptor desensitization, CREB expression, and neurogenesis, events that are typically induced by chronic antidepressant treatment in animals (Lucas *et al*, 2007). In another study, the 5-HT4 receptor partial agonist, SL650155, was also found to reduce depressive behaviors in rats as well as to increase the levels of active CREB and BDNF (Tamburella *et al*, 2009). However, the clinical usefulness of 5-HT4 receptor agonists in depression remains to be determined with proper clinical trials.

Besides several 5-HT2A and 5-HT2C receptor antagonists, such as the antidepressant, nefazodone (Fontaine, 1993), and most atypical antipsychotics (Meltzer, 1999), having clinically evidenced antidepressant effect, more recently, a considerable amount of evidence also supports the treatment of depression by blocking 5-HT7 receptors. In animal studies, blocking or inactivating 5-HT7 receptors results in an antidepressant-like effect in models of depression (Guscott *et al*, 2005; Wesolowska *et al*, 2006a,b), potentiates the physiological and behavioral actions of monoamine reuptake inhibitors (Bonaventure *et al*, 2007; Wesolowska *et al*, 2007), and normalizes circadian rhythm (Duncan *et al*, 2004; Glass *et al*, 2003;

Lovenberg *et al*, 1993; Sprouse *et al*, 2005) and sleep (Bonaventure *et al*, 2007; Hedlund *et al*, 2005; Shelton *et al*, 2009; Thomas *et al*, 2003). Clinically, several atypical antipsychotics with antidepressant properties, such as amisulpride and lurasidone, have a strong 5-HT7 receptor antagonistic effect (Stahl, 2010), supporting further investigation of putative 5-HT7 receptor antagonists for treatment of depression.

Noticeably, most existing antidepressants modulate serotonin and norepinephrine neurotransmission, and these drugs often do not typically improve depressive symptoms related to impaired dopamine action (Dunlop and Nemeroff, 2007). Earlier studies have demonstrated that amphetamine and other stimulants that increase dopamine release are effective in increasing concentration, energy, and enjoyment in depressed patients, although these agents do not have indications in the treatment of depression owing to their abuse potential. MAOIs block metabolism and increase the synaptic availability of synaptic dopamine, norepinephrine, and serotonin (Amsterdam and Bodkin, 2006; Feiger *et al*, 2006); as well bupropion increases synaptic dopamine and norepinephrine through increases in presynaptic release (Gobbi *et al*, 2003; Tomarken *et al*, 2004; Tremblay and Blier, 2006). In addition, newer triple reuptake inhibitors that block dopamine, serotonin, and norepinephrine transporters have been developed in the hope that these agents may enhance antidepressant effects and shorten the onset of treatment response. In a phase-II clinical study of depressed patients, the triple reuptake inhibitor DOV 216,303 with *in vitro* IC₅₀ values of approximately 78, 14, and 20 nM at dopamine, serotonin, and norepinephrine transporters, respectively, was compared with citalopram for its safety and tolerability. Both DOV 216,303 (50 mg, b.i.d.) and citalopram (20 mg, b.i.d.) reduced baseline depressive symptoms within a 2-week treatment period (Skolnick *et al*, 2006). This pilot trial did not evaluate the superiority of the triple *vs* the mono reuptake inhibitor; thus, the better and early onset of effect cannot be evaluated. It should be noted that, although triple reuptake inhibitors have an acute antidepressant effect in an animal behavior test (Popik *et al*, 2006; Skolnick *et al*, 2006), chronic administration of triple reuptake inhibitors may actually dampen, instead of increasing, dopamine release (Prins *et al*, 2011), a phenomenon associated with the reciprocal interactions among all three monoamine neurotransmitters. Therefore, there may be limitations with triple reuptake inhibitors in the treatment of depression.

Alternatively, direct activation of selective dopamine receptors may have a specific therapeutic value in treating depression. Pramipexole, a partial D2/D3 agonist approved for Parkinson's disease, has shown antidepressant efficacy as monotherapy in major depressive disorder, and the effect is superior to placebo and equivalent to fluoxetine (Corrigan *et al*, 2000). It has also been evaluated in bipolar depression in two 6-week, randomized, double-blind, placebo-controlled studies as adjunct treatment to mood stabilizers (Goldberg *et al*, 2004; Zarate *et al*, 2004b).

Dosed well below the average dosing for Parkinson's disease (1.7 vs 4.5 mg), the response rates were significantly higher in both studies for pramipexole vs placebo (67 vs 20% and 60 vs 9%). In a neuroimaging analysis of bipolar-II depression, pramipexole was seen to reduce normalized metabolism in frontal cortical areas (Mah *et al*, 2010), where cerebral metabolic activity is reportedly elevated in the depressed state of mood disorders (Drevets, 1999; Drevets *et al*, 1992; Mah *et al*, 2007). The findings are particularly important as they implicate dopamine receptor-targeting agents in depressive symptoms presented in both major depression and bipolar depression. Future clinical studies comparing the efficacy of dopamine agents to serotonergic and adrenergic agents in depression are in need, particularly to identify agents effective in both major depression and bipolar depression, as well as their onset of action, side-effect profile, and abuse potential.

Modulation of Glutamatergic Neurotransmission in the Treatment of Mood Disorders

Glutamate is the major excitatory neurotransmitter of the brain (Curtis and Watkins, 1961). It is synthesized from glutamine in glutamate neurons, released into synapses to activate pre- and postsynaptic glutamate receptors, and metabolized to glutamine in glial cells to be re-used for glutamate synthesis (Chaudhry *et al*, 2002). The association of glutamate neurotransmission with mood disorders has been increasingly recognized in the last decade (Paul and Skolnick, 2003). Earlier studies showed that patients with mood disorders have increased glutamate levels in the peripheral blood compartments (Altamura *et al*, 1995, 1993; Kim *et al*, 1982a, b; Mauri *et al*, 1998). Postmortem brain studies also found increased glutamate levels in the frontal cortex of patients with bipolar disorder and major depression (Hashimoto *et al*, 2007), whereas reduced glutamate and increased glutamine were found in the cerebrospinal fluid (Frye *et al*, 2007b; Levine *et al*, 2000). The altered glutamate neurotransmission in mood disorders is further demonstrated in magnetic resonance spectroscopy as recently reviewed by Yuksel and Ongur (2010). In general, the overall glutamate and glutamine signals tend to be decreased in major depressive disorder and elevated in bipolar disorder, and depressed patients show an overall pattern of a reduced glutamine/glutamate ratio. Although data are not completely consistent, it is likely that perturbed glutamate neurotransmission is a feature associated with mood disorders.

As discussed earlier, the mood-stabilizing agents, valproic acid and lamotrigine, have glutamate-modulating property. In addition, monoamine-regulating antidepressants were also found to normalize brain glutamate activity (Bonanno *et al*, 2005; Michael-Titus *et al*, 2000) and peripheral glutamate level (Maes *et al*, 1998; Mauri *et al*, 1998). More recent clinical trials have continued to support the antidepressant efficacy of glutamate-modulating drugs. Riluzole, a neuroprotective agent with FDA approval for

amyotrophic lateral sclerosis (ALS), inhibits presynaptic glutamate release (Benavides *et al*, 1985; Doble, 1996). In two preliminary open-label studies, riluzole demonstrated a significant antidepressant effect as either monotherapy or an add-on to a prior antidepressant therapy in major depressive disorder (Sanacora *et al*, 2007; Zarate *et al*, 2004a). In lithium-resistant bipolar depression, open-label addition of riluzole also showed significant clinical improvement in depressive symptoms (Zarate *et al*, 2005). In another open-label study on bipolar depression, the antidepressant effect of riluzole was associated with an increase in the glutamine/glutamate ratio in magnetic resonance spectroscopy, further suggesting that normalizing glutamate turnover by riluzole is involved in the treatment of depression (Brennan *et al*, 2010). Additionally, in a randomized, double-blind, multicenter, placebo-controlled study of 75 subjects with bipolar disorder, addition of N-acetylcysteine to usual medication over 24 weeks was reported to improve depression in the bipolar maintenance phase (Berk *et al*, 2008). Although the antioxidant dietary supplement likely has multiple actions, modulating glutamate exchange to eventually reduce the synaptic release of glutamate is one of its recognized actions (Moran *et al*, 2005).

Therefore, biochemical studies and clinical trials both suggest that modulating glutamate neurotransmission is one of the promising alternative therapeutics in mood disorders, an effect that may occur in the depressive phase of both major depressive and bipolar disorder. Glutamate activates three types of ionotropic receptors with high affinity to N-methyl-D-aspartate (NMDA), AMPA, and kainic acid (Dingledine *et al*, 1999), and a group of G-protein-coupled metabolic glutamate receptors (Conn, 2003) (Figure 2).

Evidence of NMDA receptors as a therapeutic target of depression can be traced back to 1959 when cycloserine, a partial agonist of the glycine recognition site of NMDA receptors, was reported to have an antidepressant effect (Crane, 1959). A preliminary study with amantadine, a weak NMDA antagonist, also found antidepressant efficacy (Vale *et al*, 1971). The proof-of-concept clinical study, however, was demonstrated more recently with the NMDA receptor antagonist ketamine. In the first pilot study, depressed patients who received intravenous infusion of ketamine evidenced significant improvement in depressive symptoms within 72 h of ketamine infusion (Berman *et al*, 2000). The beneficial effect of ketamine in treatment-resistant depression was further demonstrated in a landmark double-blind, randomized, placebo-controlled clinical trial (Zarate *et al*, 2006a), which involved 18 male and female participants with major depressive disorder who had experienced insufficient response with at least two different adequate antidepressant trials. Following a 2-week drug-free period, the participants received intravenous infusions of either a saline solution or ketamine hydrochloride (0.5 mg/kg) 1 week apart in a crossover assignment. The participants were rated at baseline and at 40, 80, 110, and 230 min, and 1, 2, 3,

and 7 days, after each infusion. The results were striking as participants experienced a rapid and robust antidepressant effect within 110 min of the infusion, and the effect continued through day 3. The study resulted in a large effect size (Cohen's $d = 1.46$), with 71% meeting the response and 29% meeting the remission criteria during the ketamine treatment week. In another randomized, placebo-controlled, double-blind, crossover, add-on study of treatment-resistant bipolar depression, intravenous ketamine infusion, when added to the mood stabilizer treatment, showed a robust and rapid antidepressant effect after a single intravenous dose (Diazgranados *et al*, 2010a). Therefore, ketamine has a rapid antidepressant effect in both major depressive and bipolar disorders.

Although data from ketamine trials strongly support the view that NMDA receptor blockade may exert a rapid and robust antidepressant action, a recent trial of the oral form of another NMDA receptor antagonist, memantine, did not show an antidepressant effect in major depressive disorder (Zarate *et al*, 2006b). Intravenous drug delivery, although less useful in an out-patient setting, could be beneficial for hospitalized depressed patients who require rapid response to treatment, and for emergency management of suicidality in depressed patients, a condition that has shown response to ketamine infusion (DiazGranados *et al*, 2010b). In addition, as ketamine is also an anesthetic that does not elevate the seizure threshold, supplementing standard anesthetics with low-dose ketamine (within the dose range found effective in depression trials) may facilitate a seizure response and an antidepressant effect during electroconvulsive therapy for treatment-resistant depression. Several case reports have suggested this application with ketamine (Kranaster *et al*, 2011; McDaniel *et al*, 2006; Okamoto *et al*, 2010; Ostroff *et al*, 2005), but clinical efficacy remains to be demonstrated through randomized clinical trials. It should be noted that the antidepressant effect of ketamine is rapid albeit transient. A pilot study attempting to continue the effect of ketamine using oral riluzole unfortunately failed to show sustained therapeutic benefit (Mathew *et al*, 2010). Therefore, the clinical implications of NMDA receptor antagonists for depressant remain to be fully evaluated. Ketamine infusions may cause a brief (ie, an hour or two) duration of mild perceptual distortions, which may be related to a well-known property of ketamine in inducing psychotic symptoms, especially hallucinations (Berti *et al*, 2009; Giannini *et al*, 2000). Therefore, intravenous administration of ketamine requires close monitoring in clinical settings.

In a recent proof-of-concept clinical trial, CP101606, an antagonist of the brain-enriched NR2B subunit of NMDA receptors, was found to elicit an antidepressant effect when added to paroxetine in patients with major depressive disorder who failed to respond to two earlier antidepressants (Preskorn *et al*, 2008). An intravenous injection of CP101606 reduced the depressive symptoms within 5 days of administration, and 'low-dose' CP101606 appears to have less a psychotomimetic effect than ketamine, suggesting an

improved side-effect profile with highly selective NMDA receptor antagonists (Koller and Urwyler, 2010).

Blocking NMDA receptors by systemic administration of ketamine or other NMDA receptor antagonists markedly increases glutamate release in the medial prefrontal cortex (Lopez-Gil *et al*, 2007; Moghaddam *et al*, 1997) and concomitantly increases the firing rate of pyramidal neurons (Jackson *et al*, 2004), suggesting that the action of NMDA receptor antagonists is to enhance prefrontal cortical activity. The antidepressant effect of NMDA receptor antagonists requires the action of AMPA receptors, as AMPA receptor antagonists are able to abolish the behavioral effects of NMDA receptor antagonists (Maeng *et al*, 2008; Moghaddam *et al*, 1997).

Animal studies of intracellular mechanisms of NMDA receptor antagonist have revealed that ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway in the prefrontal cortex, leading to increased levels of the postsynaptic proteins PSD95 and the GluR1 AMPA receptor subunit, and the presynaptic protein synapsin-I, as well as an increased number and function of new spine synapses (Li *et al*, 2010a). Conversely, blockade of mTOR signaling completely abolished ketamine-induced synaptogenesis and several behaviors representing depression and anxiety (Li *et al*, 2010a, 2011). In another brief report, ketamine was found to inhibit GSK3, and the antidepressant-like behavioral effect of ketamine in animals depends on the inhibition of GSK3 through an inhibitory phosphorylation (Beurel *et al*, 2011). Noticeably, both activation of mTOR and inhibition of GSK3 are linked to Akt signaling (Cross *et al*, 1995; Scott *et al*, 1998), which can also be activated by ketamine (Li *et al*, 2010a). A more recent study also found that the rapid antidepressant effect of ketamine in animals depends on BDNF protein synthesis induced by the elongation factor when neurons are at the resting state, an effect likely mediated by suppressing the calcium-dependent calmodulin kinases (Autry *et al*, 2011). Although the signaling network from the transient blocking of NMDA receptors to a rapid behavior effect remains to be elucidated, current findings suggest the involvement of suppression on calcium-dependent signaling followed by activation of neurotrophic signaling pathways (Figure 2).

Besides NMDA receptor antagonists, potential antidepressant effects of AMPA receptor modulators has also been proposed; AMPA receptor allosteric potentiators have shown potent antidepressant action in preclinical studies (Alt *et al*, 2006). The AMPA receptor agents have been reported to have a neurogenic and neuroprotective action, which may contribute to their effect in mood regulation (Zarate and Manji, 2008). In animal behavioral studies, several metabolic glutamate receptor antagonists selective for the metabolic glutamate receptors mGlu2/mGlu3 (Chaki *et al*, 2004; Yoshimizu *et al*, 2006), mGlu5 (Li *et al*, 2006; Molina-Hernandez *et al*, 2006), and mGlu7 (O'Mahony *et al*, 2010; Wieronska *et al*, 2010) have shown promising antidepressant effect. It has been proposed that metabolic glutamate receptor ligands may impact a neural network

that downregulates NMDA receptor function and enhances AMPA receptor signaling (Pilc *et al*, 2008).

Modulators of Acetylcholine Receptors in the Treatment of Depression

The cholinergic hypothesis of depression is an earlier model that proposed an association of a predominantly cholinergic over an adrenergic tone for depression, and the reverse for mania (Janowsky *et al*, 1972). The hypothesis was supported by a series of studies on animals and of humans showing that cholinergic challenge, such as with the acetylcholinesterase inhibitor physostigmine, causes depressive symptoms (El-Yousef *et al*, 1973; Riemann *et al*, 1994; Rosic and Bignami, 1970; Steinberg *et al*, 1997). However, potential use of anticholinergic drugs as antidepressants is much less developed, despite some evidences showing that agents modulating cholinergic receptors have mood-regulating properties. While promising new drugs targeting cholinergic receptors are discussed in other chapters of this review issue, below we reveal cholinergic drugs that have undergone trials as antidepressant treatment.

In early clinical trials evaluating the role of the cholinergic system in cognitive function in depressed patients, investigators noticed a reduction of depressive symptoms following administration of the muscarinic cholinergic receptor antagonist scopolamine (Gillin *et al*, 1991; Newhouse *et al*, 1988). The antidepressant efficacy of scopolamine has been replicated in two recent clinical trials: one includes both major depressive disorder and bipolar depression (Furey and Drevets, 2006), and the other is focused on major depressive disorder (Drevets and Furey, 2010). Importantly, the trials used an intravenous infusion of scopolamine in three intermittent periods, and each infusion elicited a potent antidepressant effect. The effect was prolonged even after scopolamine had been crossed over to placebo. This suggests that scopolamine has an acute and sustained antidepressant effect that differs from monoamine modulators. Noticeably, the acute antidepressant effect of scopolamine is similar to that observed with the glutamate receptor antagonist ketamine (Berman *et al*, 2000; Zarate *et al*, 2006a), which also has an acute onset of action after intravenous infusion. As delayed onset of therapeutic action is a major drawback of monoamine-modulating antidepressants, rapid antidepressant efficacy after intravenous administration may find unique applications in the treatment of depression in the emergency setting. However, muscarinic receptor antagonists have unavoidable negative effects in cognition and memory (Molchan *et al*, 1992; Sunderland *et al*, 1985; Vitiello *et al*, 1997), especially in elder patients, thus clinical application of muscarinic receptor antagonists for the treatment of depression appears to be pessimistic, unless age, prodromal cognitive deficit, and pseudodementia of depression have been carefully taken into consideration.

Scopolamine is a non-selective muscarinic receptor antagonist, whereas there are five subtypes of muscarinic

receptors, among which M1, M3, and M5 couple to Gq protein, which mediates receptor activation to phospholipase-C/protein kinase-C (PKC) and calcium signaling, whereas M2 and M4 couple to the inhibitory G-protein (Gi) protein, which inhibits adenylyl cyclase and reduces cAMP production (Brann *et al*, 1993) (Figure 2). In earlier small clinical trials, the central M1 muscarinic receptor-selective antagonist biperiden was found to have an antidepressant effect (Beckmann and Moises, 1982; Kasper *et al*, 1981), but the effect was not replicated in a later trial (Gillin *et al*, 1995). Therefore, available data are not sufficient to project which subtype of muscarinic receptor has a major role in the antidepressant effect of anticholinergic drugs, and which one contributes to the cognitive side effect.

The role of nicotinic cholinergic receptors in depression and treatment has recently been reinforced by the large body of studies on cigarette smoking and cessation. Epidemiological analyses have shown that people with major depressive disorder have a higher rate of smoking than the general population (Kalman and Smith, 2005). People with depression also have more difficulties to stop smoking, and are likely to relapse to a depressive episode during smoking cessation (Dani and Harris, 2005; Hughes, 2007). These analyses appear to suggest that continued cigarette use may help ameliorate depressive symptoms. The direct contribution of nicotine in ameliorating depression has further been demonstrated in a clinical trial in mildly depressed non-smokers, where chronic transdermal nicotine administration for 4 weeks, but not acute nicotine administration, was found to reduce depressive symptoms (McClernon *et al*, 2006).

Nicotinic acetylcholine receptors are pentameric ligand-gated ion channels (Figure 2) that are grouped into α -subunits ($\alpha 2-\alpha 10$) and β -subunits ($\beta 2-4$). In the neural system, the α - and β -subunits form heteromeric receptors that bind to agonists with high affinity (in nM concentrations), among which $\alpha 4\beta 2$ receptors account for >90% of the high-affinity nicotinic receptors in the brain (Whiting and Lindstrom, 1986). The low-affinity receptors are homomeric α -receptors that bind to agonists with lower affinity (μ M concentrations). The physiological contributions of nicotinic receptors to neurotransmission, signaling, and behavior are not completely understood, but their predominant role is thought to be in modulating the neurotransmission of dopamine, glutamate, GABA, and norepinephrine (Benowitz, 2009). Owing to the prominent role of nicotine in addiction, a large body of research has been focused on the dopaminergic modulating effect of nicotinic receptors. Systemic administration of nicotine was found to induce dopamine neuron firing and long-lasting dopamine release from the ventral tegmental area (VTA) onto nucleus accumbens (Gao *et al*, 2010; Imperato *et al*, 1986; Schilstrom *et al*, 1998). This effect of nicotine is mediated by either the $\beta 2$ or the $\alpha 7$ subunit of nicotinic receptors, which initially causes the rapid enhancement of glutamate neurotransmission, which contributes to an induction of glutamatergic synaptic long-term potentiation

in VTA dopamine neurons (Gao *et al*, 2010; Mansvelder *et al*, 2002; Mansvelder and McGehee, 2000). With the increasingly recognized roles of dopamine and glutamate in mood disorders, the well-recognized modulating effect of nicotine on dopamine/glutamate neurotransmission could contribute to the antidepressant action of nicotine.

The potential antidepressant effect of activating nicotine receptors, however, has been challenged by an earlier preclinical study showing that not only nicotine, but the nicotinic receptor antagonists mecamylamine and varenicline also potentiated the acute antidepressant-like effect of monoamine reuptake inhibitors in the forced swim test in mice (Popik *et al*, 2003). As a single-agent treatment, however, studies on animals did not find an acute antidepressant effect of nicotine or selective nicotinic receptor agonists; instead, the antidepressant-like effects of the nicotinic receptor antagonist mecamylamine have been replicated in several animal behavioral studies (Andreasen and Redrobe, 2009; Mineur *et al*, 2007; Rabenstein *et al*, 2006). However, clinical trial data demonstrating an antidepressant effect of mecamylamine in humans are still lacking, except one report showing that 8-week mecamylamine treatment augmented the antidepressant effect of SSRI in patients who are refractory to SSRI monotherapy (George *et al*, 2008), but the effect was not significantly different between mecamylamine and placebo augmentation. Several trials of mecamylamine monotherapy and augmentation in depression have been conducted (Clinicaltrial.gov), which are expected to provide conclusive information, although data have not yet been reported. If confirmed for treatment of depression, nicotinic receptor antagonists could be promising as unlike scopolamine, there is little evidence showing a cognitive impairment effect when mecamylamine is administered alone (Ellis *et al*, 2006; Voss *et al*, 2010).

The question remains to be addressed is why nicotine receptor activation by nicotine and blocking by mecamylamine both appear to have some antidepressant effect in preclinical or clinical studies. It has been hypothesized that desensitization of nicotinic receptors after prolonged activation may be responsible for the antidepressant effect of nicotine (Mineur and Picciotto, 2010). Additionally, the antidepressant effect of a nicotinic receptor antagonist is likely to be receptor subtype-selective; for example, the $\alpha 4\beta 2$ receptor antagonist varenicline, a drug with indication in smoking cessation, has shown acute antidepressant effect in animals (Rollema *et al*, 2009). In an open-label study of 14 subjects with depression and nicotine dependence, varenicline augmentation to antidepressants or mood stabilizers was reported to be associated with significant improvement in mood (Philip *et al*, 2009); however, effects on mood in studies investigating the smoking cessation effect of varenicline are inconsistent. Most likely that balanced nicotinic receptor activity is the key for mood regulation, as shown in several pre-clinical studies investigating the antidepressant efficacy of cytosine, a partial agonist at the $\alpha 4\beta 2$ nicotinic receptors

(Mineur *et al*, 2009; Mineur *et al*, 2007). In animals, the nicotinic receptor agonist cytisine not only reduces immobility in forced swim and tail suspension tests, but it also changes the novelty-suppressed feeding and light-dark box preference, tests that represent both anxious and depressive behaviors. Therefore, the clinical efficacy of nicotinic receptor modulators in depression remains to be investigated in large clinical trials, whereas better understanding of the pharmacological mechanisms of action of each nicotinic receptor subtype will be an important aspect for successfully applying nicotinic receptor modulators, either agonists or antagonists, in the treatment of depression.

Sleep and Circadian Regulation in the Treatment of Mood Disorders

Sleep disturbance has long been known as a core symptom of both depression and mania. A typical symptom of sleep disturbance in mania is feeling less need for sleep. In depression, insomnia and hypersomnia are frequent symptoms, with the latter considered characteristic of atypical depression and bipolar depression. It is also evident that some types of mood disturbances present with a seasonal pattern, as exemplified by seasonal depression and bipolar mania. Sleep is partly regulated by both homeostatic balance and the endogenous circadian clock (Fuller *et al*, 2006). However, sleep is not the only sign of circadian dysregulation in mood disorders. Patients with mood disorders also undergo disturbance of other circadian-regulated functions such as weight change, metabolic syndrome, hormone dysregulation, and cardiovascular diseases.

The circadian clock is an endogenous biological system that determines the temporal pattern of many physiological processes such as sleep, temperature, feeding, hormone release, and rhythmic activities of the heart and other organs (Bass and Takahashi, 2010). The primary circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Welsh *et al*, 2010), where light signals from the retina, endogenous hormones, and neurotransmitters, as well as environmental stimuli, converge to reset the phase of the circadian clock. Inside the SCN and throughout the body, a cluster of circadian genes turn on and off in response to transcriptional and translational feedback regulation, as well as external signals to reset the on/off switch (Cermakian and Sassone-Corsi, 2000; Dunlap, 1999; Reppert and Weaver, 2002). Among the most studied circadian genes are positive activators BMAL1 and CLOCK/NPAS2. They regulate the transcriptional expression of *Period* (*Per1* and *Per2*) and *Cryptochromes* (*Cry1* and *Cry2*), which feedback-suppress their own expression by negatively regulating BMAL1 and CLOCK/NPAS2. *Per* and *Cry* transcription can also be acutely upregulated in response to light at night such that light exposure at early night extends the current circadian cycle and light exposure at late night advances the next cycle (Ashmore and

Sehgal, 2003). In addition, a secondary feedback loop is formed when CLOCK-BMAL1 activate the transcription of a nuclear orphan receptor Rev-erb α whose protein product feeds back to repress Bmal1 transcription.

Genetic and animal studies have recently provided evidence showing that variation of circadian genes can be etiologic to mood disorders. A single-nucleotide polymorphism (SNP) in the 3'-flanking region of CLOCK (3111T/C; rs1801260) has been found in more than one study to be associated with bipolar disorder (Benedetti *et al*, 2007, 2008, 2003; Lee *et al*, 2010). Recent studies testing behavioral changes in animal models have also revealed that manic-like and drug-seeking behaviors are observed in mice carrying a mutant dominant-negative CLOCK gene whose protein products cannot activate transcription (Roybal *et al*, 2007). Therefore, circadian regulation is increasingly considered a therapeutic component in mood disorders.

Improving sleep is an important treatment component in mood disorders. For example, sleep deprivation has a transient antidepressant effect (Hemmeter *et al*, 2010). But this approach has limited therapeutic value as patients would rapidly return to depression after cessation of a one-time treatment. Light therapy was initially used for treating seasonal depression to normalize light-dark cycle, but has also been increasingly found beneficial to other types of depression (Golden *et al*, 2005; Rosenthal *et al*, 1984), possibly through effects on normalizing circadian rhythms. In fact, most mood-stabilizing agents, such as atypical antipsychotics, valproate, and some antidepressants, have sleep-normalizing effects, although the mechanisms of action vary largely. Lithium also normalizes circadian rhythms, which may be related to its therapeutic effects (Klemfuss, 1992). As noted earlier, lithium is an inhibitor of GSK3. In *Drosophila*, the ortholog for GSK3, Shaggy, was first reported to phosphorylate the circadian gene *Timeless*, resulting in premature nuclear translocation of the PERIOD/TIMELESS heterodimer and a shortened period of the *Drosophila* circadian locomotor activity cycle (Martinek *et al*, 2001). In mammalian tissues, the activity of GSK3 β shows a circadian rhythm, and the dynamically regulated GSK3 β was found to interact with and regulate PER2 translocation into the nucleus and *Per2* gene expression (Iitaka *et al*, 2005). GSK3 β was also found to phosphorylate and stabilize a negative component of the secondary autoregulatory feedback loop (Rev-erb α) in cultured cells, and lithium treatment leads to rapid proteasomal degradation of Rev-erb α and activation of BMAL1 (Yin *et al*, 2006). Although deleting GSK3 or inhibition of GSK3 activity might alter circadian rhythm in a sophisticated pattern that is still not completely understood (Hirota *et al*, 2008; Iitaka *et al*, 2005; Kaladchibachi *et al*, 2007; Martinek *et al*, 2001), it has been shown that some circadian gene-regulating effects of GSK3 can be suppressed by lithium, suggesting that normalizing the circadian clock, at least partly through inhibition of GSK3 β , may contribute to the mood-stabilizing effect of lithium. The mood-regulating effect of GSK3 will be discussed later in more detail, to support the

development of selective GSK3-inhibiting agents for the therapeutics of mood disorders; among the potential effects of GSK3 inhibitors, normalizing circadian rhythms could be particularly interesting and important.

As dysregulation of circadian rhythm has been recognized as a major contributor or a sequel of mood disturbance, the promising clinical trial data on the high-affinity melatonin receptor agonist plus the 5-HT2C receptor antagonist agomelatine have raised significant interest in the hope that this represents a new mechanism of pharmacological treatment of depression. In clinical trials testing its efficacy in major depressive disorders, agomelatine has demonstrated significant short-term (6–8 weeks) (Kennedy and Rizvi, 2010; Loo *et al*, 2002a,b; Stahl *et al*, 2010; Zajecka *et al*, 2010) and sustained (6 months) (Goodwin *et al*, 2009) antidepressant effects relative to placebo, as well as evidence of relapse prevention. Although agomelatine has a short half-life of 2 h, this does not seem to prevent it from reducing the clinical symptoms of depression. Instead, the onset of the antidepressant action of agomelatine appeared to be early (at 1–2 weeks) when compared with venlafaxine or sertraline (Kasper *et al*, 2010; Kennedy *et al*, 2008). Additionally, agomelatine is found to restore disturbed sleep-wake patterns early in treatment (Kasper *et al*, 2010; Quera-Salva *et al*, 2007), which can be an additional benefit to patients with depression.

The primary pharmacological action of agomelatine, although not assessed as a major outcome clinically, is to phase advance circadian rhythms and improve sleep quality (Quera-Salva *et al*, 2010; Van Reeth *et al*, 1998). A multi-synaptic pathway from the retina to the pineal gland through the SCN drives rhythmic melatonin synthesis and release, which are negatively regulated by photic stimulation at night (McNulty *et al*, 1994; Morgan *et al*, 1994). The resulting nocturnal peak in melatonin acts on the melatonin receptors residing in the SCN. The MT1 and MT2 melatonin receptors couple to the Gi (Stankov *et al*, 1992); activation of these receptors therefore results in the inhibition of cAMP production and reduction of SCN neuron firing (Figure 2). Agomelatine has been shown to activate the MT1 and MT2 receptors in the SCN to normalize the circadian rhythm (Ying *et al*, 1996). Besides being an agonist of MT1 and MT2, agomelatine has also been found to be a 5-HT2C receptor antagonist with moderate receptor affinity (Millan *et al*, 2010). As neither melatonin itself nor putative 5-HT2C receptor antagonists have significant antidepressant efficacy, there is a possibility that a joint action on melatonin receptors and 5-HT2C receptors is necessary to elicit an antidepressant effect by agomelatine.

Currently, agomelatine has been tested primarily as an antidepressant in major depressive disorder. With its circadian-normalizing and 5-HT2C receptor-blocking effects, the efficacy of agomelatine in alleviating symptoms of bipolar depression is worthy of future clinical trials. In a placebo-controlled trial of ambulatory type-I bipolar disorder patients, another melatonin-mimicking drug ramelteon was reported to improve the global ratings of

depressive symptoms (McElroy *et al*, 2011), although ramelteon seems to have limited efficacy in insomnia in bipolar disorder (McElroy *et al*, 2011; Schaffer *et al*, 2011). Therefore, the mechanisms of melatonin-mimetic drugs in the treatment of mood disorders remain to be further investigated, as normalizing circadian rhythm may not be the sole action of these drugs.

In the completed clinical trials, agomelatine showed little impact in treatment-induced sexual dysfunction or weight gain (Goodwin *et al*, 2009; Kennedy and Rizvi, 2010). These favorable side-effect profiles would have significant clinical values as these are major drawbacks of many existing antidepressants and mood-stabilizing agents. However, one should be cautious about this impression when the physiological action of either melatonin receptors or 5-HT_{2C} receptors is taken into account. Melatonin receptors are also expressed in the pituitary and peripheral endocrine tissues. Although melatonin supplementation does not seem to change diurnal hormone levels, there is evidence showing that melatonin-mimetic drugs may change the levels of prolactin (Richardson and Wang-Weigand, 2009), which could raise a concern of reproductive dysfunction. The weight gain effect of atypical antipsychotics has been thought to be associated with their antagonistic action on 5-HT_{2C} receptors (De Luca *et al*, 2007), but this adverse effect of atypical antipsychotics did not become a significant concern until they had been marketed for years. Additionally, 5-HT_{2C} receptor antagonist-induced weight gain appears to be associated with genetic variations (De Luca *et al*, 2007), which would require replication studies with a sufficient sample size to confirm this effect. Therefore, it might be premature to conclude a neutral effect on sexual function and weight by agomelatine until longitudinal observation data are made available.

The wakefulness-promoting agent modafinil has indications for excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder (Minzenberg and Carter, 2008; Myrick *et al*, 2004). Although stimulant-like in its actions, the exact mechanism of action is unknown, and unlike conventional stimulants, modafinil appears to have low abuse liability (Myrick *et al*, 2004). Adjunctive modafinil 100–200 mg daily, in a placebo-controlled study has been shown to be effective in reducing depressive symptoms in bipolar disorder (Frye *et al*, 2007a). This initial study was the impetus for a larger controlled evaluation of armodafinil, the R-enantiomer of modafinil, in bipolar depression (Calabrese *et al*, 2010). In this study, patients who received armodafinil along with lithium, valproic acid, or olanzapine showed greater improvement in depressive symptoms as seen in the total score of the Inventory of Depressive Symptomatology—Clinician Rated version (IDS-C₃₀) (15.8 ± 11.57) compared with placebo treatment (-12.8 ± 12.54). With this rating scale, the improvement of depressive symptoms appeared to be superior after 2 weeks of armodafinil treatment, which may suggest an early onset of effect. Adverse events reported

with armodafinil include frequent insomnia, but the study did not conduct formal tests on circadian measures.

Although the exact mechanism of action remains to be elucidated, modafinil has pharmacological action as an enhancer of norepinephrine and dopamine release (Mitchell *et al*, 2008; Wisor and Eriksson, 2005), and it may also elicit a wake-promoting effect by enhancing histamine and glutamate neurotransmission (Minzenberg and Carter, 2008). In animal studies, the wake-promoting effect of modafinil does not adjust the circadian phase nor does it alter light-and novel wheel-induced phase shifts (Webb *et al*, 2006). Instead, it decreases the amount of novel wheel-stimulated running, such that less activity is required for the same size phase shift. Therefore, modafinil may increase the sensitivity of the circadian pacemaker to non-photic stimuli, and when combined with behavioral strategies, may have potential for promoting circadian clock-resetting (Webb *et al*, 2006). If this observation is further supported in additional animal and human studies, application of modafinil as an adjunctive to a non-photic circadian regulator, such as a melatonergic agonist or an exercise programme, should be tested with a design to enhance rhythmic circadian regulation in patients with depression, particularly in the context of bipolar disorder.

Targeting Signal Transduction for Mood Stabilization

Activation or blocking neurotransmitter receptors results in an altered intracellular signal transduction process, which proceeds to regulation of neuron activity, gene expression, and other downstream effects (Figures 1 and 2). A signal transduction protein kinase that has drawn significant interest in mood disorder research is PKC, a large family of serine/threonine kinases with 12 isoforms in mammals (Mellor and Parker, 1998) (Figures 1 and 2). Since the first report of elevated PKC activity in platelets of patients during bipolar mania (Friedman *et al*, 1993), the association of this enzyme with bipolar disorder has been demonstrated from different aspects of preclinical and clinical studies that have been comprehensively summarized in several expert reviews (Diaz-Granados and Zarate, 2008; Manji and Chen, 2002; Manji and Lenox, 1999; Zarate and Manji, 2009). Particularly important is that both lithium and valproic acid have a PKC-inhibitory effect (Chen *et al*, 1994; Hahn *et al*, 2005; Wang and Friedman, 1989), suggesting a role of PKC as a therapeutic target in the treatment of bipolar mania. Additionally, several isoforms of PKC can be activated by Gq protein-coupled receptors such as $\alpha 1$ -adrenergic receptor, M1/3 muscarinic cholinergic receptors, and metabolic glutamate receptors (discussed in the above sections). PKC is also a downstream acceptor of tyrosine kinase receptors that are activated by growth factors and neurotrophins (Rankin *et al*, 2008; Zirrgiebel *et al*, 1995). Although not discussed in detail in this review, it is widely known that neurotrophins have major contributions in the pathophysiology of mood disorders (Duman and Monteggia, 2006;

Martinowich *et al*, 2007; Post, 2007; Warner-Schmidt and Duman, 2008).

As tamoxifen, an antiestrogen agent for breast cancer suppression, has a PKC-inhibitory property (O'Brian *et al*, 1985), this clinically available agent has been tested for its efficacy in bipolar mania in several pilot clinical studies. Among them, two studies investigated the efficacy of tamoxifen monotherapy in double-blind, placebo-controlled clinical trials ($n = 16$ and $n = 66$, respectively) (Yildiz *et al*, 2008; Zarate *et al*, 2007). Although the sample sizes were small, 3-week tamoxifen treatment was associated with significant improvement in manic symptoms. Other studies have also tested the effect of tamoxifen as an adjunct to lithium or divalproex (Amrollahi *et al*, 2011; Bebchuk *et al*, 2000; Kulkarni *et al*, 2006), all of which demonstrated superior anti-manic effect of tamoxifen.

In their original study, O'Brian *et al* (1985) reported that tamoxifen inhibits the activity of partially purified PKC extracted from brain tissue. Although tamoxifen did not directly interfere with the catalytic unit of the enzyme, it was suggested that the lipophilic tamoxifen competes with phospholipid for the regulatory domain of the enzyme (O'Brian *et al*, 1985; Su *et al*, 1985) (Figure 1). The PKC-inhibitory effect of tamoxifen in intact cells (Horgan *et al*, 1986) is relatively selective as it has no inhibitory effect on cAMP-dependent protein kinase-A (Spacey *et al*, 1990), indicating that inhibition of PKC is a potential mechanism of tamoxifen action.

Clinical trial of tamoxifen for bipolar mania is perhaps the first proof-of-concept investigation of protein kinase inhibitors in the treatment of mood disorders, although several issues about this hypothesized treatment remain to be resolved. The obvious antiestrogen effect of tamoxifen cannot be ruled out in clinical studies unless selective PKC inhibitors are found to have similar anti-manic actions. The secondary effect of hormonal changes after tamoxifen treatment in mood regulation also remains to be clarified in studies using other antiestrogenic agents that lack PKC-inhibitory action as comparative control. Additionally, the adverse effect of the antiestrogen in disrupting female hormone regulation and developing malignancy set the limit on using this agent in the general population for treating bipolar mania. Its long-term mood-stabilizing effect has not been investigated, possibly because of a concern for its disruptive action in hormonal regulation. Despite the logistical concerns about tamoxifen, current data from tamoxifen studies encourage developing PKC inhibitors for potential clinical application in mood disorders.

Over 50 years of successful clinical use and mechanistic studies of lithium have further suggested that regulation of intracellular signaling beyond membrane receptors contributes to the mood-stabilizing actions of lithium. Among many investigated lithium actions, GSK3 has arisen as a promising therapeutic target of mood disorders. GSK3 (Embi *et al*, 1980), including GSK3 α and GSK3 β , are paralogous protein kinases that are universally expressed. In brain, GSK3 regulates many aspects of neuronal function

such as gene expression, neurogenesis, synaptic plasticity, neuronal structure, and neuronal survival and death (Doble and Woodgett, 2003; Frame and Cohen, 2001; Jope and Johnson, 2004). Unlike many other protein kinases, both GSK3 isoforms are constitutively active (ie, partially active in the absence of activation), and they are regulated predominantly in an inhibitory manner (Doble and Woodgett, 2003) by several protein kinases (Cross *et al*, 1995; Fang *et al*, 2000; Goode *et al*, 1992; Li *et al*, 2000) that phosphorylate GSK3 at an N-terminal serine residue, serine-21 of GSK3 α and serine-9 of GSK3 β (Stambolic and Woodgett, 1994; Sutherland and Cohen, 1994; Sutherland *et al*, 1993) (Figure 1).

GSK3 was identified as a site of lithium action in 1996 when two independent research groups (Klein and Melton, 1996; Stambolic *et al*, 1996) reported that lithium selectively competes with magnesium that is required for the kinase activity of GSK3 (Ryves and Harwood, 2001). Importantly, the direct inhibition by lithium, which has a low potency at an IC₅₀ of 2 mM, can be robustly enhanced by increasing the inhibitory phosphorylation of the N-terminal serine of GSK3 in animal brains and human peripheral blood mononuclear cells (PBMCs) at therapeutically relevant lithium concentrations (Chalecka-Franaszek and Chuang, 1999; De Sarno *et al*, 2002; Li *et al*, 2007a), including evidence that the level of phospho-serine-9 of GSK3 β is eightfold higher in bipolar patients stabilized on lithium treatment than in healthy controls who are not exposed to lithium (Li *et al*, 2007a). This secondary effect of lithium on GSK3 could be mediated by the inhibition of the upstream regulator Akt, inhibition of protein phosphatase-1, or disruption of a β -arrestin/Akt/PP2A complex (Beaulieu *et al*, 2008a; Chalecka-Franaszek and Chuang, 1999; Pan *et al*, 2011; Zhang *et al*, 2003).

GSK3 is not only a biological target of lithium, it is also one of the few identified molecules that can be inhibited by many existing pharmacological agents used in mood disorders. These include the anticonvulsant mood stabilizer valproate (Aubry *et al*, 2009; Chen *et al*, 1999; De Sarno *et al*, 2002; Kim *et al*, 2005; Kozlovsky *et al*, 2006; Lamarre and Desrosiers, 2008; Phiel *et al*, 2001; Werstuck *et al*, 2004), most atypical antipsychotics (Alimohamad *et al*, 2005; Li *et al*, 2007b; Roh *et al*, 2007), and the monoamine reuptake inhibitor antidepressants fluoxetine and imipramine (Beaulieu *et al*, 2008b; Li *et al*, 2004). All these agents indirectly increase the level of phospho-serine of GSK3, resulting in the inactive status of the enzyme (Li and Jope, 2010b). These pharmacological studies on animals have recently been reinforced in the clinical treatment of bipolar mania, where an 8-week combination treatment of acutely manic patients with lithium or valproic acid plus an atypical antipsychotic caused a significant increase in serine phosphorylation of GSK3 in PBMCs (Li *et al*, 2010c). Therefore, inhibition of GSK3 is a common mechanism of action shared by a variety of drugs that treat mood disorders, and GSK3 serves as a target for both anti-manic and anti-depressive treatments.

The common action of mood disorder treatments on GSK3 concurs with evidence showing that GSK3 is regulated by neuromodulators involved in mood disorders. BDNF, a neurotrophin upregulated by antidepressants (Duman and Monteggia, 2006; Schmidt and Duman, 2007), phosphorylates the N-terminal serine of GSK3 by activating Akt (Cross *et al*, 1995; Mai *et al*, 2002), resulting in the inhibition of GSK3 (Johnson-Farley *et al*, 2006; Mai *et al*, 2002). GSK3 is also under the regulation of serotonin and dopamine. In the mouse brain, enhancing serotonergic activity by *d*-fenfluramine or activation of 5-HT1A receptors increases the serine phosphorylation of GSK3 in several brain regions (Li *et al*, 2004). Conversely, in serotonin-deficient mice that carry mutation of the tryptophan hydroxylase-2 gene associated with major depression (Zhang *et al*, 2005), serine phosphorylation of GSK3 is low and GSK3 activity is elevated (Beaulieu *et al*, 2008b). By contrast, elevation of extracellular dopamine in dopamine transporter-knockout mice was shown to reduce the serine phosphorylation of GSK3 in the striatum, an effect that was reversed by the administration of a dopamine D2 receptor antagonist (Beaulieu *et al*, 2004). Regulation of GSK3 by D2 receptors involves a protein complex including the scaffolding protein β -arrestin2, protein phosphatase-2 (PP2A), and Akt (Beaulieu *et al*, 2005), where Akt is inactivated and was incapable of phosphorylating and inhibiting GSK3.

Besides being regulated by phosphorylation, GSK3 activity can be buffered by its association with protein partners. An example of this is its association with the axin protein complex (Behrens *et al*, 1998; Rubinfeld *et al*, 1996) where it phosphorylates β -catenin and facilitates β -catenin degradation by the proteasome (Davies *et al*, 2001; Henderson, 2000). Activation of Wnt, another signaling pathway that is associated with mood disorders (Gould *et al*, 2007; Inkster *et al*, 2010; Zandi *et al*, 2008), results in the dissociation of the axin complex (Doble *et al*, 2007), which terminates the protein complex-dependent action of GSK3.

In animal studies, GSK3 has been shown to be an important regulator of mood-related behaviors. Transgenic mice overexpressing constitutively active GSK3 β show hyperactivity in the open field test and increased acoustic startle response (Prickaerts *et al*, 2006), suggesting that excessive GSK3 β could be a precipitating factor in heightened locomotor activity and sensory responses. The behavioral effects of active GSK3 have been further characterized recently (Polter *et al*, 2010a) in mice with serine-to-alanine mutations that block the inhibitory serine phosphorylation of both GSK3 α and GSK3 β (McManus *et al*, 2005). A striking feature of these mice is that they show increased susceptibility to both amphetamine-induced hyperactivity and stress-induced depressive-like behaviors. This reinforces the postulation that abnormal activation of GSK3 under conditions resembling lack of regulation by neuromodulators is a risk factor for developing mood-related behavioral disturbances. Indeed, a postmortem study of suicide subjects reported increased activity of

GSK3 β in depressed but not in non-depressed samples (Karege *et al*, 2007). In PBMCs from a small group of human subjects, the phosphorylated serine of both GSK3 α and GSK3 β was found to be lower in symptomatic bipolar patients than healthy controls (Polter *et al*, 2010a), and the reduction is significantly correlated with the severity of manic and depressive symptoms. Therefore, human studies support evidence from animal behavior studies indicating that GSK3 activity is affected in mood disorders.

Conversely, GSK3 β haploinsufficient (lacking one copy of the gene encoding GSK3 β) mice have reduced immobility in the forced swim test, increased exploratory activity (O'Brien *et al*, 2004), and reduced amphetamine-induced hyperactivity (Beaulieu *et al*, 2004). Reducing GSK3 β in these animals is also effective in normalizing the impaired tail suspension behavior in serotonin-deficient mice that otherwise have increased GSK3 activity (Beaulieu *et al*, 2008b). Similarly, GSK3 α -knockout mice show decreased exploratory activity, decreased immobility time in the forced swim test, and reduced aggressive behavior (Kaidanovich-Beilin *et al*, 2009), suggesting that inhibition of both GSK3 α and GSK3 β is important in behavior regulation. Significantly, these data also indicate that targeting inhibition of GSK3 may achieve mood stabilization, preventing the behavioral disturbance of not only mania but also depression.

Therefore, ample data from pharmacological, neurochemical, and behavioral studies provide strong evidence that GSK3 is a highly promising therapeutic target in the treatment of mood disorders. However, while lithium inhibits GSK3, it also has other intracellular effects; therefore, inhibition of GSK3 may be a component of the intracellular lithium actions, but it may not explain the full effect of lithium in mood disorders. Tests of selective GSK3 inhibitors are needed. Currently available GSK3 inhibitors are mostly small-molecule ATP competitors (Cohen and Goedert, 2004; Martinez *et al*, 2006; Meijer *et al*, 2004). Among them, AR-A014418, SB216763, indirubin-3-monoxime, alsterpaullone, TDZD, NP031115, and BIP-135 have been reported to either cause an antidepressant-like behavioral effect or ameliorate hyperactivity, or have both effects in animal behavior tests (Beaulieu *et al*, 2004; Chen *et al*, 2011; Gould *et al*, 2004; Pan *et al*, 2011; Rosa *et al*, 2008), suggesting that these GSK3-selective inhibitors have mood-regulating effects.

However, there may be legitimate difficulties in developing therapeutic agents by inhibiting protein kinases. Protein kinase inhibitors may have non-targeting effect as their selectivity is relative to their affinity to one or more protein kinases. As for GSK3, its wide distribution in non-neuronal tissues may cause side effects. GSK3 also have significant physiological functions as a constitutively active protein kinase. Extreme suppression of brain GSK3 activity may therefore perturb normal brain function regulated by GSK3. To increase the selectivity of GSK3 inhibitors, substrate-mimicking peptides that block GSK3 access to its substrates is an alternative approach. A small peptide GSK3 inhibitor,

L803-mts, when administered through intracerebroventricular injection in rats, has been shown to reduce immobility in the forced swim test (Kaidanovich-Beilin *et al*, 2004). More recently, virus-guided GSK3 β -shRNA, when directly delivered into the hippocampus, is shown to exhibit an antidepressant effect in an animal model of chronic depression (Omata *et al*, 2011), suggesting a brain regional effect of GSK3 inhibitors. All these GSK3 inhibitors have only been tested in animal models, whereas the clinical implications of these GSK3-targeting approaches remain to be evaluated for their efficiency and safety in mood stabilization.

FUTURE DIRECTIONS

Most currently available pharmacological treatments of mood disorders are related to mechanisms of action discovered decades ago. After a long fallow period, there has been important recent progress in testing drugs with novel mechanisms of action. However, substantial obstacles in advancing the pharmacological therapy of mood disorders remain to be addressed. Ideally, new drug development needs to be advanced to (1) design effective clinical trials to test the specific effects of drugs; (2) identify biomarkers for treatment selection and outcome prediction; and (3) target specific molecular mechanisms involved in mood disorder pathophysiology.

As noted by Gelenberg *et al* (2008), modifications of traditional clinical trial designs are needed for mood disorders, particularly studies in depression. These changes include (1) broadening the inclusion criteria to involve patients typically treated in the clinical settings in which a drug is likely to be used; (2) the use of measures (eg, the Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979) or the Quick Inventory of Depressive Symptomatology (Rush *et al*, 2003)) that are more sensitive to change; and (3) conducting moderator analyses to identify specific subgroups most likely to respond to a given treatment; moderators of treatment response may include clinical characteristics, genetics, or other biomarkers (Kraemer *et al*, 2003). Given the heterogeneity of mood disorders, a study design with broad inclusion of all types of depression (major depression, dysthymia, bipolar-I and II depression, depression with substantial medical comorbidity such as diabetes) may delineate clinical response patterns with increased translational appeal. Furthermore, owing to the multiple etiologies of mood disorders, it is to be expected that a single treatment will not target the entire spectrum of conditions. Traditionally, clinical trials of mood disorders use standardized depression and mania rating scales that assess core mood symptoms, which do not provide a comprehensive assessment of the spectrum of mood symptoms. When new drugs targeting different receptor pharmacology or molecular mechanisms are developed, classical assessment of mood disorders may not be sufficient to identify new treatment with unique mechanisms as hypothesized or tested in preclinical studies.

Several examples of successfully using dimensional rather than traditional assessment of mood have emerged in clinical trials. For example, Tomarken *et al* (2004) compared the effects of bupropion *vs* placebo by using the Mood and Anxiety Symptom Questionnaire, derived from the tripartite of Clark and Watson (1991), which assesses mood in three dimensions: positive affect (corresponding to mood symptoms such as low energy, motivation, and enjoyment), general distress (more closely related to the psychological symptoms of anxiety as seen in generalized anxiety disorder), and somatic anxiety (physiological arousal, which is found in panic disorder). Bupropion exerted a more robust effect on the positive affective dimension than either general distress or somatic anxiety, which is consistent with its effects in the catecholamine system (Shelton and Tomarken, 2001). Similar effects have been shown with modafinil augmentation trial in antidepressant non-responders (Fava *et al*, 2005, 2007); modafinil was shown to improve symptoms of fatigue and daytime somnolence in treatment-resistant depression. By contrast, Tang *et al* (2009) showed that the SSRI paroxetine has robust effects on the personality/temperament dimensions of neuroticism (an enduring trait of negative emotional reactions to real or anticipated stress) and extraversion relative to placebo. In fact, the drug-placebo differences on the personality dimensions were much more robust than that seen with the Hamilton Rating Scale for Depression (Hamilton, 1960). The effects of an SSRI on the neuroticism dimension may be consistent with the constraining effects of the SSRI class on the amygdala response to perceived threat (Sheline *et al*, 2001). Therefore, clinical assessments targeting the hypothesized mechanism of drug action should be routinely included in mood disorder clinical trials for the proof-of-concept new drug development with a unique mechanism of action.

Another outstanding need in mood disorder treatment is to identify biological tests with predictive ability to assist treatment selection for individual patients who may have different response to drugs. Pharmacogenomic approaches have produced only very modest associations accounting for a very little proportion of the variance in outcome (Binder and Holsboer, 2006; Keers and Aitchison, 2010). Alternative biomarker approaches targeting specific mechanisms of action of treatments may be more successful. For example, several studies (Sen *et al*, 2008; Yasui-Furukori *et al*, 2011) have shown that the plasma level of BDNF increases in response to antidepressant treatment, which occurs as early as 2 weeks of treatment (Yasui-Furukori *et al*, 2011). The findings in human samples are valid as they are consistent with findings in brains of animals treated with antidepressants (Duman and Monteggia, 2006). If a correlation between the increase in serum BDNF and the degree of clinical response to antidepressant treatment can be determined, BDNF measurement may serve as a surrogate marker to predict individual response to monoamine-regulating antidepressants. When new treatments with different mechanisms are under development, earlier biomarker identification even during the clinical trial

TABLE 1 Representative Cellular Molecules with Potential Roles as Mood Disorder Therapeutic Targets

Classification	Name	Selected references
Growth factors	Brain-derived neurotrophic factor (BDNF)	(Duman et al, 1997; Post, 2007; Sen et al, 2008)
	Vascular endothelial growth factor (VEGF)	(Elfving et al, 2010; Greene et al, 2009; Warner-Schmidt and Duman, 2008)
	Fibroblast growth factors (FGF)	(Turner et al, 2006)
Protein kinases	Glycogen synthase kinase-3 (GSK3)	(Li and Jope, 2010b)
	Protein kinase-C (PKC)	(DiazGranados and Zarate, 2008)
	Extracellular signal-regulated kinase (Erk)	(Creson et al, 2009; Engel et al, 2009)
Intracellular proteins	p11	(Alexander et al, 2010; Svenningsson et al, 2006)
	Bcl-2 and associated proteins	(Kosten et al, 2008; Lien et al, 2008; Salvadore et al, 2009; Zhou et al, 2005)
Transcription factors	CREB	(Carlezon et al, 2005; Nibuya et al, 1996)
	DeltaFosB	(Ohnishi et al, 2011; Vialou et al, 2010)
	β-Catenin	(Gould et al, 2007, 2008)
	FoxO3a	(Liang et al, 2006; Mao et al, 2007; Polter et al, 2009; Zheng et al, 2002; Zhu et al, 2004)
	CLOCK	(McClung, 2007; Roybal et al, 2007)

period may facilitate biomarker application in the prediction of treatment response to each group of drugs with specific mechanisms. Genetic and peripheral biomarkers, when combined with a selected brain-imaging test, would be a valuable subjective indicator of treatment response in addition to clinical assessment.

As reviewed in this article, various new drugs that target non-monoamine systems have been tested in preclinical and clinical studies as alternative treatment for mood disorders. It is notable that most drugs in clinical trials act at cell-surface neurotransmitter receptors, which may regulate several signal transduction pathways (Figures 1 and 2) and elicit more than one physiological response. Alternatively, drugs specifically targeting signal transduction and other intracellular elements may emerge as important therapeutic approaches. In preclinical studies, many intracellular molecules have shown prominent roles in the neuropathology of mood disorders (see Table 1 for some examples), and some may have potential to be developed as therapeutic targets for mood disorders. However, outstanding challenges remain as most these intracellular molecules are ubiquitously expressed in both neural and non-neural tissues, and activation or inhibition of some has a brain region-specific effect. It is more likely that before successfully developing drugs targeting these important mood-regulating molecules, research is needed to understand the neuron- and brain region-specific function of each one of them. This review did not discuss these molecules in detail as drugs targeting them have not been investigated for clinical implication, but this is one of the promising future areas of research for advanced treatment of mood disorders.

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