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Perspective

Novel Drugs and Therapeutic Targets for Severe Mood Disorders

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Monoaminergic-based drugs remain the primary focus of pharmaceutical industry drug discovery efforts for mood disorders, despite serious limitations regarding their ability to achieve remission. The quest for novel therapies for unipolar depression and bipolar disorder has generally centered on two complementary approaches: (1) understanding the presumed therapeutically relevant biochemical targets of currently available medications, and using that knowledge to design new drugs directed at both direct biochemical targets and downstream targets that are regulated by chronic drug administration; and (2) developing pathophysiological models of the illness to design therapeutics to attenuate or prevent those pathological processes. This review describes several promising drugs and drug targets for mood disorders using one or both of these approaches. Agents interacting with non-catecholamine neurotransmitter systems with particular promise for unipolar and bipolar depression include excitatory amino acid neurotransmitter modulators (eg, riluzole, *N*-methyl-D-aspartate antagonists, and AMPA receptor potentiators) and neuropeptide antagonists (targeting corticotropin releasing factor-1 and neurokinin receptors). Potential antidepressant and mood-stabilizing agents targeting common intracellular pathways of known monoaminergic agents and lithium/mood stabilizers are also reviewed, such as neurotrophic factors, extracellular receptor-coupled kinase (ERK) mitogen-activated protein (MAP) kinase and the bcl-2 family of proteins, and inhibitors of phosphodiesterase, glycogen synthase kinase-3, and protein kinase C. A major thrust of drug discovery in mood disorders will continue efforts to identify agents with rapid and sustained onsets of action (such as intravenous administration of ketamine), as well as identify drugs used routinely in non-psychiatric diseases for their antidepressant and mood-stabilizing properties.
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WHY INVESTIGATE NEW TARGETS BEYOND MONOAMINES?

Despite an explosion in psychiatric neuroscience research in the past decade, there is consensus regarding a significant 'pipeline' problem in neuropsychopharmacology (Agid *et al*, 2007; Pangalos *et al*, 2007). Given the high lifetime prevalence of DSM-IV mood disorders (20.8%), with first onset often in childhood or adolescence (Kessler *et al*, 2005), the public health urgency of identifying safe and more effective treatments for these common and disabling conditions is clear. For unipolar and bipolar disorder, and the commonly comorbid anxiety disorders, there have been very few significant innovations and no genuine breakthrough drugs in the past 2 decades (Spedding *et al*, 2005). Novel therapeutic strategies that accelerate speed of onset, enhance efficacy, and tolerability, while addressing core pathophysiological features of these illnesses are needed.

The limitations of current approaches to drug discovery in neuropsychiatric disorders have been extensively scrutinized (Roth *et al*, 2004; Wong and Licinio, 2004; Spedding *et al*, 2005; Berton and Nestler, 2006; Agid *et al*, 2007). Much of the previous (and current) focus of investigation for mood disorders regards the biology and neural circuitry most relevant to the monoaminergic systems (serotonin (5-HT), norepinephrine (NE), and dopamine (DA)), given the therapeutic benefit of the selective 5-HT reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and dopaminergic medications (Mann, 2005; Dunlop and Nemeroff, 2007; Nestler and Carlezon, 2006). A recent modernization of the classical monoamine theory of depression has posited that elevated density of monoamine oxidase A (MAO-A) (the enzyme that metabolizes 5-HT, NE, and DA) is the primary monoamine-lowering process during a major depressive episode, while monoamine transporter density variability plays a secondary role in influencing loss of

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specific monoamines, explaining symptomatic heterogeneity during major depressive episodes (Meyer *et al*, 2006). Areas of active investigation in monoamine biology include (1) catecholamine depletion studies using acute tryptophan depletion, phenylalanine/tyrosine, or alpha-methyl-para-tyrosine (see Ruhe *et al*, 2007 for review); (2) *in vivo* brain imaging studies of specific receptors and transporters for these neurotransmitters (eg, Oquendo *et al*, 2007; Parsey *et al*, 2006a, b; Bhagwagar *et al*, 2006; Moses-Kolko *et al*, 2007); (3) cerebrospinal fluid (CSF) and neuroendocrine challenge studies; (4) postmortem studies; and more recently, (5) large-scale genetic association studies (Hu *et al*, 2007). Inasmuch as the phenotype of depression is heterogeneous, biological investigations of monoamine systems in diverse patient groups has hindered the ability to reliably uncover abnormalities and has stymied identification of biomarkers. Contradictions in the literature, rather than reflecting minimal involvement of monoaminergic systems in disorder pathophysiology, likely reflect heterogeneity of biological substrates. Phenotypic contributors to mood disorder heterogeneity, which likely impact expression of monoamines (and response to SSRIs and similar drugs), include sex, age of onset (early onset *vs* mid-life *vs* late-onset), race/ethnicity, subtype (melancholic *vs* atypical *vs* dysthymic), current mood state (euthymic *vs* depressed), chronicity of illness, previous number of episodes, family history of psychopathology, and axis I–III disorder comorbidity (Trivedi *et al*, 2006).

Thus, while SSRIs and similar monoaminergic drugs are the mainstays of pharmacological treatment for mood disorders, their limitations in sustaining disorder remission are increasingly apparent. The first phase of the STAR*D study, the largest effectiveness study of its kind in 'real world' patients, measured the efficacy of the SSRI citalopram in outpatients with unipolar depression ($n = 2876$). Remission rates were 28%, a remission rate similar to that achieved in standard randomized placebo-controlled acute efficacy trials (Trivedi *et al*, 2006). As the presence of residual symptoms is a strong predictor of relapse or recurrence (Keller, 2004), optimal therapeutic strategies require a focus on achieving and sustaining remission, by presumably addressing core pathophysiological processes. Non-monoaminergic biological systems have received increasing attention from translational researchers for their potential therapeutic application for mood disorders. The most actively pursued drug targets for unipolar depression include amino-acid neurotransmitter receptors and transporters, neuropeptides (corticotropin-releasing factor (CRF), substance P), neurotrophic factors (brain-derived neurotrophic factor (BDNF)), and steroid receptors/hormones (glucocorticoid receptor, DHEA, testosterone, melatonin; see Hasler *et al*, 2004; Berton and Nestler, 2006; Martinowich *et al*, 2007 for reviews). It is noteworthy, however, that despite numerous potentially novel targets, relatively few non-monominergic-based drugs will gain FDA approval by the end of this decade, while additional monoaminergic medications, with minimal advantages over existing drugs, will likely gain regulatory approval over the next few years. Table 1 lists medications in phase II and III clinical trials for unipolar major depression (accessed on www.clinicaltrials.gov on 24 July 2007).

Table 1 Medications in US FDA Clinical Trials for Unipolar Major Depression

Mechanism	Name	Company
Phase III novel mechanism drugs		
β3-Adrenoreceptor agonist	Amibegron	Sanofi-Aventis
GR-II antagonist	Mifepristone	Corcept Therapeutics
Melatonin M1/M2 agonist, 5-HT2C/2B-selective	Agomelatine	Novartis
NK-1 antagonist	Casopitant	GlaxoSmithKline (GSK)
NK-1 antagonist	L-759274	Merck
NK-2 antagonist	Saredutant	Sanofi-Aventis
Phase III monaminergic-based drugs		
D2 and 5-HTA antagonist	Quetiapine SR	AstraZeneca
SNRI	Milnacipran	Cypress Bioscience
Partial D2 agonist, 5-HT1A partial agonist, 5-HT2A antagonist	Aripiprazole	Bristol-Myers Squibb
5-HT2 antagonist and 5-HT reuptake inhibitor	Trazodone CR	CSC
5-HT1A partial agonist	Gepirone ER	Fabre-Kramer, GSK
5-HT reuptake inhibitor and 5-HT1A partial agonist	Vilazodone	Genaissance
SNRI	Desvenlafaxine	Wyeth
Phase II novel mechanism drugs		
CRF-1 antagonist	CP 316,311	Pfizer
CRF-1 antagonist	GW876008	GSK
CRF1 antagonist	CP-316, 311	Pfizer
CRF1 antagonist	BMS-562086	Bristol-Myers Squibb
GR antagonist	ORG 34517/ 34850	Organon
Mitochondrial benzodiazepine receptor agonist	AC 5216	Dainippon/ Novartis
NNR antagonist	TRIDMAC	Targacept
NK-1 antagonist	TAK-637	TAP
NK-1 antagonist	R 673	Nippon Roche
NK-1 antagonist	Vestipitant, GW597599	GSK
NMDA (NR2B) glutamate antagonist	Traxoprodil	Pfizer
Pentapeptide analog of melanocyte-inhibiting factor (MIF-1)	Nemifitide	Tetragenex
Phenylalanine derivative	YKP 10A, R228060	Janssen, SK
V1B antagonist	SSR149415	Sanofi-Aventis
Phase II monaminergic-based drugs		
Bis-aryl-sulphanyl modulator: 5-HT modulator	Lu AA21004	Lundbeck
DA/NE/5-HT reuptake inhibitor	DOV 216,303	DOV
DA/NE/5-HT reuptake inhibitor	DOV 21,947	DOV/Merck
DA/NE/5-HT reuptake inhibitor	NS 2359	GSK
DA/NE/5-HT reuptake inhibitor	DOV 21947	DOV/Merck

Table 1 Continued

Mechanism	Name	Company
DA/NE/5-HT reuptake inhibitor	GSK372475, NS2359	GSK, NeuroSearch
Dopamine (D2/D3) agonist	Pramipexole	Boehringer Ingelheim
NERI	NERI IV	Eli Lilly
Partial D2 agonist	Pardoprunox	Solvay
5-HT1A agonist and 5-HT2 antagonist	Adatanserin	Wyeth
5-HT1A agonist, sigma antagonist	PRX-00023	Epix
5-HT1B and 5-HT1D antagonist	Elzasonan hydrochloride	Pfizer
5-HT1A partial agonist	MN-305	MediciNova
Sigma and 5-HT1A agonist	OPC 14523	Otsuka
SNRI	R-sibutramine metabolite	Sepracor
SRI, 5-HT2 agonist, 5-HT1A and 5-HT1D agonist	TGBA01AD	Fabre-Kramer

Abbreviations: CRF, corticotropin-releasing factor; DA, dopamine; FDA, Food and Drug Administration; GR, glucocorticoid receptor; 5-HT, serotonin; NE, norepinephrine; NERI, selective norepinephrine reuptake inhibitor; NK, neurokinin; NMDA, *N*-methyl-D-aspartate; NNR, neuronal nicotinic receptor; V1B, vasopressin1B.
Source: www.clinicaltrials.gov (accessed on 24 July 2007). Table may not be comprehensive of every US FDA registered phase II and III medication trial for unipolar depression. The Table does not include augmentation studies, complementary and alternative medications, or neuromodulation/devices.

In this paper, we highlight several promising areas for therapeutics for mood disorders (unipolar depression and bipolar disorder) based upon two complementary approaches:

(1) Understanding the presumed therapeutically relevant biochemical targets of medications currently in use, and using that knowledge to design new drugs directed at these targets. This includes not only direct biochemical targets, but also downstream targets that are regulated by chronic drug administration (ie, consistent with the clinical temporal profile; Gould *et al*, 2004a, b).
(2) Understanding the pathophysiology of the illness, and using that knowledge to design therapeutics to attenuate or prevent those pathological processes (Quiroz *et al*, 2004). As space limitations do not permit an exhaustive discussion of every promising candidate using both strategies, we emphasize compounds with particularly high potential for clinical translation.

AGENTS INTERACTING WITH NON-CATECHOLAMINE NEUROTRANSMITTER SYSTEMS

Amino-Acid Neurotransmitter Modulators

Glutamate, the major excitatory neurotransmitter in the brain, is ubiquitous in the mammalian CNS, where it is used in up to 60% of synapses. The emerging interest in glutamate-modulating agents derives from both a pathophysiological perspective regarding amino-acid neurotransmitters' role in mood disorders as well as evidence that conventional antidepressants have effects on specific glutamate receptor subtypes (Manji *et al*, 2003; Charney and Manji, 2004). Recent pathophysiological hypotheses proffer a view of dynamic regional amino-acid transmitter dysfunction in severe, recurrent mood disorders, with implications for experimental therapeutics that target-specific ionotropic or metabotropic receptors, glial glutamate transporters, or vesicular glutamate release (Kugaya and Sanacora, 2005; Zarate *et al*, 2003; Sattler and Rothstein, 2007; see Figure 1, pathways c–f). One prominent model for unipolar depression proposes that disrupted glial cell function in structures relevant to emotional processing such as amygdala, observed in postmortem mood disorder samples (Hamidi *et al*, 2004), may result in decreased uptake of glutamate, with a resultant elevation of extracellular glutamate levels (Kugaya and Sanacora, 2005). Disruptions in glutamate (Glu)–glutamine (Gln) neuronal–glial cycling are believed to cause decreased glutamate release and decreased cortical GABA, examined *in vivo* in human subjects using techniques such as ^{13}C-MRS (Shen, 2006; Mason *et al*, 2007). A reduction in glial cell function would result in decreased flux through the Glu/Gln and GABA/Gln cycles, findings that are consistent with reduced rates of Glu/Gln cycling and lowered cortical GABA concentrations in individuals with MDD (Kugaya and Sanacora, 2005; Sanacora and Saricicek, 2007). Microarray analysis has demonstrated significant dysregulation of a specific subset of genes encoding the astroglial high-affinity glutamate transporters SLC1A2 (EAAT2; GLT1) and SLC1A3 (EAAT1; GLAST); glutamate-ammonia ligase (glutamine synthetase); and various subunits of glutamate receptors and $GABA_A$ receptors in anterior cingulate (area 24) and left dorsolateral prefrontal cortex (areas 9 and 46) (Choudary *et al*, 2005), lending support for regionally specific abnormalities in glutamate function in mood disorders.

The impairment in glial uptake of Glu, and conversion to Gln, would lead to an elevation of extracellular Glu during intense neuronal activity, and serve to activate extracellular *N*-methyl-D-aspartate (NMDA) receptors associated with various forms of excitotoxicity (Pittenger *et al*, 2007). Changes in extrasynaptic Glu concentrations can have wide-ranging effects on diverse physiological functions, including activation of signal transduction pathways involved in the regulation of neurotrophic factors, neuroplasticity, and cellular resilience (Pittenger *et al*, 2007; see Figure 1). GABAergic involvement in the pathophysiology and treatment of mood disorders is equally compelling, and supported by preclinical studies showing stress-related changes in GABAergic function, GABAergic effects of existing antidepressant medications, antidepressant/mood-stabilizing efficacy associated with GABAergic drugs, and robust GABAergic abnormalities and genetic associations in depressed patients (see Sanacora and Saricicek, 2007 for recent review).

Antidepressants/mood stabilizers that impact primarily glutamate receptors such as NMDA receptor antagonists, metabotropic glutamate receptor (mGluR) agonists and antagonists, and positive modulators of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors have

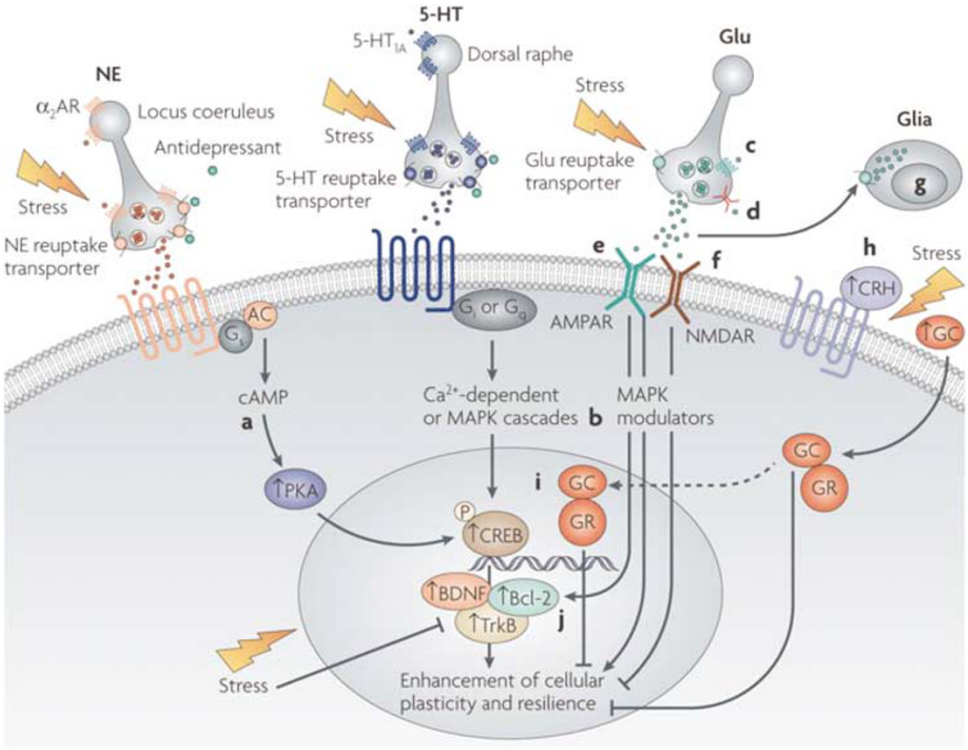

Figure 1 Plasticity regulators as targets for the development of novel agents for the treatment of mood disorders. This figure depicts the multiple targets by which neuroplasticity and cellular resilience can be increased in mood disorders. (a) Phosphodiesterase inhibitors increase the levels of pCREB; (b) MAP kinase modulators increase the expression of the major neurotrophic protein Bcl-2; (c) mGluR II/III agonists modulate the release of excessive levels of glutamate; (d) drugs such as lamotrigine and riluzole act on Na^+ channels to attenuate glutamate release; (e) AMPA potentiators upregulate the expression of BDNF; (f) NMDA antagonists like ketamine and memantine enhance plasticity and cell survival; (g) novel drugs to enhance glial release of trophic factors and clear excessive glutamate may have utility for the treatment of depressive disorders; (h) CRF antagonists and (i) glucocorticoid antagonists attenuate the deleterious effects of hypercortisolemia, and CRF antagonists may exert other beneficial effects in the treatment of depression via non-HPA mechanisms; (j) agents which upregulate Bcl-2 (eg, pramipexole, shown to be effective in bipolar depression; Zarate *et al*, 2004b). These distinct pathways have convergent effects on cellular processes such as bioenergetics (energy metabolism), neuroplasticity, neurogenesis, resilience, and survival. Nature Reviews Drug Discovery. Modified and reproduced with permission from Charney and Manji (2004).

demonstrated antidepressant-like properties, with potential common downstream mechanisms of action (Paul and Skolnick, 2003; Zarate *et al*, 2003; Sanacora *et al*, 2003; Mathew *et al*, 2005b; see Figure 1). Alterations in neural plasticity in critical limbic and reward circuits, mediated by increasing postsynaptic AMPA to NMDA throughput, may represent a convergent mechanism for therapeutics of severe mood disorders (Schloesser *et al*, 2008; Figure 1, pathways e, f). In the sections below we discuss several glutamate-modulating approaches that may hold particular promise for unipolar and bipolar depression.

Riluzole (Major Depressive Disorder And Bipolar Depression)

Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is a neuroprotective agent that is the only FDA-approved medication for amyotrophic lateral sclerosis (ALS), although median survival is only prolonged by about 2–3 months (Miller *et al*, 2007). Two open-label studies support the potential utility of riluzole in treatment-resistant unipolar depression (Zarate *et al*, 2004a; Sanacora *et al*, 2007), and one open-label add-on study found improvements in bipolar depression (Zarate *et al*, 2005). Interestingly, the patients who responded to riluzole tended to be in remission (ie, almost symptom-free), suggesting that there may be a subgroup of mood disorder patients for whom glutamatergic strategies have considerable utility. Riluzole has complex mechanisms of action; among its actions, it inhibits release of glutamate through inhibition both of voltage-dependent sodium channels and of P/Q-type calcium channels, enhances glutamate reuptake, and upregulates AMPA receptors (reviewed in Zarate *et al*, 2006b; Mathew *et al*, 2005b; see Figure 1, pathway d). Riluzole modulates neuroplasticity via stimulation of growth factor synthesis such as BDNF (Mizuta *et al*, 2001; Katoh-Semba *et al*, 2002), promotion of neuritogenesis, neurite branching, and neurite outgrowth (Shortland *et al*, 2006), increasing concentrations of the neuronal marker *N*-acetyl-aspartate in hippocampus (Mathew *et al*, in press), and enhancement of surface expression of the hippocampal AMPA receptor subunits (GluR1 and GluR2) (Du *et al*, 2007). The latter process is implicated in the regulation of activity-dependent synaptic strength and postsynaptic receptor responsiveness (Du *et al*, 2007).

Riluzole's efficacy has also been reported for patients with generalized anxiety disorder (GAD) (Mathew *et al*, 2005a; Mathew *et al*, in press). The relationship between GAD and mood disorders is particularly strong (Moffitt *et al*, 2007; Kessler *et al*, 2005), and patients with 'anxious depression'

likely represent a common and valid subtype of mood disorder (Fava *et al*, 2004, 2006) and are less likely to achieve remission with standard SSRIs (Trivedi *et al*, 2006). One intriguing mechanism that could explain riluzole's anxiolytic efficacy is evidence that at higher concentrations, riluzole strongly potentiated postsynaptic $GABA_A$ receptor function in cultured hippocampal neurons (He *et al*, 2002). Commonly used anxiolytics such as benzodiazepines bind to and allosterically interact with $GABA_A$ receptors, which mediate most fast inhibitory neurotransmission. Thus, riluzole may confer antidepressant and anxiolytic activity through numerous mechanisms, and randomized placebo-controlled studies are warranted.

NMDA Receptor Antagonists (Major Depressive Disorder And Bipolar Depression)

There is substantial evidence that NMDA receptor antagonists have antidepressant properties (Krystal, 2007). Chronic treatment with NMDA antagonists such as MK-801 and AP-7 resulted in antidepressant-like behavioral effects in models such as chronic mild stress, learned helplessness, footshock-induced aggression, and olfactory bulbectomy (reviewed in Paul and Skolnick, 2003). Chronic, but not acute, treatment with NMDA antagonists also resulted in reductions in density of forebrain β-adrenoreceptors (Paul *et al*, 1992; Maj *et al*, 1993) and 5-HT_2 receptors (Papp *et al*, 1994). Similar to monoamine-based antidepressants, NMDA antagonists given to animals processed in the forced swim test resulted in rapid downregulation of forebrain β-adrenoceptors (Wedzony *et al*, 1995). Repeated administration of conventional antidepressants has been found to alter the expression of mRNA that encodes NMDA receptor subunits (Boyer *et al*, 1998), through expression of BDNF (Brandoli *et al*, 1998).

The above preclinical reports provided a sound rationale for recent exploratory work using NIMDA receptor antagonists in mood disorder patients. Ketamine, a high-affinity non-competitive NMDA antagonist, has been used as a standard anesthetic agent for many years both in pediatrics and in adults, with doses as high as 2 mg/kg intravenous (i.v.). Two placebo-controlled studies of a single subanesthetic dose of i.v. ketamine (0.5 mg/kg infusion over 40 min) in unipolar depression (Berman *et al*, 2000; Zarate *et al*, 2006a, b), reported rapid although transient antidepressant efficacy. Euphoric and psychotomimetic side effects were observed acutely (2–4 h following i.v. administration), but were temporally distinct from the amelioration of core depressive symptoms, which in some cases persisted for up to 1 week. It was shown more recently in rodent models that AMPA receptor throughput is required for the antidepressant-like effect of ketamine, and that ketamine may result in rapid antidepressant effect by enhancing AMPA relative to NMDA throughput in critical neuronal circuits (Du *et al*, 2006; Maeng *et al*, 2007; Figure 1, pathway f).

In contrast to the dramatic effects observed in these two i.v. ketamine studies, a placebo-controlled study of the low-to-moderate-affinity non-competitive NMDA antagonist memantine (oral dosing) did not show antidepressant effects (Zarate *et al*, 2006c). While higher-affinity NMDA antagonists may be required for antidepressant efficacy, i.v. administration may also be an important factor. Important next steps for i.v. ketamine studies in mood disorders include (1) dose-finding studies of i.v. ketamine, as all studies thus far have used fixed 0.5 mg/kg dosage, in an attempt to balance antidepressant efficacy with side effects; (2) repeated dose administration studies; (3) investigations of whether particular medications may be used in combination with i.v. ketamine to potentiate (and extend) the antidepressant effects; and (4) studies in bipolar depression. Given ketamine's potential for acute psychotomimetic side effects, however, more selective subtype NMDA antagonists, such as NR2B receptor subtype, with lower liability for these side effects, will continue to be explored (Zarate *et al*, 2007a). Indeed, the NR2B antagonist Ro 25-6981 had antidepressant-like properties in the forced swim test (Maeng *et al*, 2007). From a safety perspective, this compound also has not been associated with vacuolization in rodents (Gil *et al*, 2002), in contrast to the reversible vacuolization at high doses observed with noncompetitive NMDA antagonists such as ketamine and dizocilpine (Olney *et al*, 1989).

AMPA Receptor Potentiators/Ampakines (Major Depressive Disorder)

AMPA receptors are a subfamily of ionotropic glutamate receptors that mediate the fast component of excitatory neurotransmission, and which, like NMDA receptors, are involved in learning and memory. Several classes of compounds can allosterically modulate AMPA receptors. These compounds (so-called AMPA receptor-positive modulators or AMPA receptor potentiators, ARPs) do not activate AMPA receptors themselves, but slow the rate of receptor desensitization and/or deactivation in the presence of an agonist. Several AMPA receptor potentiators in development have demonstrated antidepressant effects in animal models of depression, including exposure to inescapable stressors, the forced swim test, the tail-suspension-induced immobility test, and learned helplessness models (reviewed in Zarate *et al*, 2006b). In contrast to traditional antidepressants, this group of compounds does not appear to affect the extracellular concentration of monoamines; however, these drugs can enhance the neurotrophic actions of BDNF mRNA and protein in primary neuronal cultures and in rat brain (Bleakman *et al*, 2007; Figure 1, pathway e). No placebo-controlled clinical trials in mood disorder patients have been published to date; a phase II trial of an AMPA receptor potentiator for major depression was recently halted due to preclinical toxicity (www.clinicaltrials.gov identifier NCTG00113022).

NEUROPEPTIDES AS THERAPEUTIC TARGETS FOR MAJOR DEPRESSION

Neuropeptides are short-chain amino acids that act as neurotransmitters in brain circuits implicated in mood and anxiety regulation. Recognition of the large number of neuropeptide targets and the role of stress-related neuropeptides in preclinical models has prompted investigation into the clinical utility of small-molecule neuropeptide

modulators. Below we review two classes of neuropeptide receptor antagonists that are well represented in phase II and III RCTs of unipolar depression (Table 1): (1) corticotropin-releasing factor-1 (CRF1) receptor, also known as corticotropin-releasing hormone (CRH), antagonists, and (2) neurokinin (NK) receptor antagonists.

Corticotropin-Releasing Factor Antagonists

Over 20 years of preclinical research have suggested that the 41-amino-acid peptide CRF is an important mediator of the stress response, coordinating the neuroendocrine, autonomic, immune, and behavioral responses to stress, while hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis has been associated with subgroups of patients with major depression (Holsboer, 2000). Hypothalamic and extrahypothalamic neurons containing CRF1 and CRF2 receptors are located throughout key brain stem, limbic, and cortical regions implicated in affective and anxiety, with CRF1 the predominate subtype in limbic regions and in pituitary regulation of HPA axis activity (Valdez, 2006). Animal models of early life stress have been associated with hyperactivity of CRF neurons, and direct CRF administration into CNS is associated with depression and anxiety-like symptoms (Gorman *et al*, 2002). Clinical evidence for the putative role of CRF in patients with major depression includes (1) increased concentrations of CRF in CSF (Nemeroff *et al*, 1984); (2) blunted adrenocorticotropin (ACTH) response to systemic injection of exogeneous CRF, suggesting pituitary CRF receptor downregulation due to chronic CRF hypersecretion (Holsboer *et al*, 1984; Gold *et al*, 1984); (3) postmortem studies showing increased CRF and/or messenger RNA (mRNA) expression in hypothalamic paraventricular nucleus, brain stem, and frontal cortex (reviewed in Heim *et al*, in press); and (4) characteristic escape from suppression with elevated ACTH and cortisol response to the combined dexamethasone/CRF test (Ising *et al*, 2005).

To date, one CRF1 receptor antagonist (R121919) has been tested in an open-label clinical trial for major depression (Zobel *et al*, 2000), with improvements noted in depressive and anxiety symptoms. Hepatotoxicity ended the clinical development of this particular compound, although several CRF1 receptor antagonists are currently in worldwide development for major depression (see Table 1; Figure 1, pathway h) and for anxiety disorders, including post-traumatic stress disorder and social phobia.

Neurokinin Receptor Antagonists

Substance P is the most abundant brain tachykinin (a class, which includes NK A and B among others), and is the endogeneous ligand for the neurokinin 1 (NK-1) receptor (Ebner and Singewald, 2006). The initial interest in this neuropeptide and receptor family for mood and anxiety conditions reflected its extensive colocalization with monoamine neurotransmitters (Ebner *et al*, 2004) and abundant expression in stress neural circuitry. Genetic or pharmacologic blockade of NK-1 receptors were observed to induce many of the same long-term neural effects as standard antidepressants on cell signaling molecules such as BDNF and hippocampal neurogenesis (Blier *et al*, 2004; van der Hart *et al*, 2005), providing the rationale for experimental therapeutic trials in mood and anxiety disorders (Herpfer and Lieb, 2005). Despite the promising preclinical data, a recent pooled analysis of five 8-week randomized, double-blind, placebo-controlled, multicenter studies of the NK-1 receptor antagonist aprepitant in over 2500 patients with major depression failed to demonstrate efficacy (Keller *et al*, 2006). Notably, paroxetine 20 mg was used as an active comparator for three of the trials and demonstrated benefit over placebo on primary outcomes, suggesting that the trials had appropriate assay sensitivity. Despite the setback for this particular compound, several NK-1 antagonists remain in active development for unipolar depression (Table 1).

Saredutant (SR 48968) is a selective non-peptide NK-2 receptor antagonist that blocks the effects of NK A, the endogenous ligand for NK-2. This compound has shown antidepressant and anxiolytic-like effects in preclinical models (Salomé *et al*, 2006) and has progressed the furthest in clinical development. Of four phase III studies conducted in major depression, two showed statistically significant results and two studies were not statistically significant *vs* placebo; the drug manufacturer anticipates an application for regulatory approval in 2008 (source: Sanofi-Aventis press release, 17 September 2007).

COMMON INTRACELLULAR PATHWAYS OF MONOAMINERGIC DRUGS AND MOOD STABILIZERS/LITHIUM RELEVANT TO NOVEL THERAPEUTICS

Evidence that antidepressants and mood stabilizers exert major effects on signaling pathways regulating cellular plasticity has reshaped views about the neurobiological underpinnings of these disorders (Manji *et al*, 2001; D'Sa and Duman, 2002; Nestler *et al*, 2002; Schloesser *et al*, 2008). In this section we review several therapeutic targets and common pathways that monoaminergic antidepressants and mood stabilizers/lithium impact either directly or indirectly, with relevance for novel unipolar and bipolar disorder therapeutics.

BDNF/Growth Factors (Major Depressive Disorder)

Genetic/neurodevelopmental factors, repeated affective episodes (and likely elevations of glucocorticoids), and illness progression may all contribute to the impairments of cellular resilience, volumetric reductions, and cell death/atrophy observed in mood disorders (Charney and Manji, 2004). According to the neurotrophic hypothesis of depression (Duman and Monteggia, 2006), decreased expression of BDNF and other growth factors likely contributes to mood disorders, while upregulation of BDNF and its receptor TrkB may be a critical component of all antidepressants' actions (Figure 1, pathway j). Structural imaging studies in unipolar depression have found a decrease in the gray matter volume of multiple areas of the orbital, medial, and dorsolateral prefrontal cortex, with the most prominent reduction reported in the left (but not right) subgenual prefrontal cortex (see Drevets, 2001, 2007). An increase in ventricular size also has been consistently reported in

patients with bipolar disorder, and progressive gray matter loss in hippocampal, fusiform, and cerebellar regions (Moorhead *et al*, 2007; see Beyer *et al*, 2004; Manji *et al*, 2003 for reviews). The trophic effects are postulated to reverse illness-related atrophic changes, thereby reinstating the neurochemical throughput in critical circuitry regulating affective, cognitive, motoric and neurovegetative functions (Charney and Manji, 2004). Human phase I/II trials of recombinant methionyl human BDNF have already been undertaken, wherein the BDNF was administered by intrathecal infusion to patients with ALS (Ochs *et al*, 2001). Unfortunately, treatment-limiting side effects were encountered at higher doses, precluding further study. The recent report of dysregulation of several fibroblast growth factor (FGF) system transcripts in frontal cortical regions of brains from human subjects with major depression suggests that this growth factor family may also represent an important target for the development of novel therapeutics (Evans *et al*, 2004).

Erk MAP Kinase Pathway and Bcl-2 (Bipolar Disorder)

Lithium and mood stabilizers such as valproate activate the extracellular receptor-coupled kinase (ERK) mitogen-activated protein (MAP) kinase pathway, which is an intracellular signaling cascade implicated in neuroplasticty (Schloesser *et al*, 2008). An increasing number of strategies are being investigated to develop small-molecule switches for protein–protein interactions, which have the potential to regulate MAP kinase cascades, and interactions between homo- and heterodimers of the Bcl-2 family of proteins (Figure 2, pathway b; see Schloesser *et al*, 2008 for recent review). Both TrkA and TrkB utilize the phosphatidylinositol-3 kinase (PI3K)/Akt and ERK MAP kinase pathways to bring about their neurotrophic effects (see Schloesser *et al*, 2008). The ERK MAP kinase cascade also increases the expression of Bcl-2 via its effects on cAMP response element-binding protein (CREB).

It has been hypothesized that lithium's antidepressant effects might be associated with its upregulation of Bcl-2 (Charney and Manji, 2004). Bcl-2 has traditionally been viewed as a 'long-term neuroprotective protein'; however, Bcl-2 is a key regulator of mitochondrial function, and there is a growing appreciation of the diverse functions that mitochondria play in regulating integrated CNS function. Thus, increasing evidence suggests that mitochondrial Ca^{2+} sequestration has 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 synaptic strength of neuronal circuitry mediating complex behaviors. Bcl-2 attenuates apoptosis by sequestering proforms of death-driving cysteine proteases (called caspases) by preventing the release of mitochondrial apoptogenic factors such as calcium, cytochrome *c*, and apoptosis-inducing factor (AIF) into the cytoplasm, and by enhancing mitochondrial calcium uptake (Charney and Manji, 2004; Schloesser *et al*, 2008). It is also noteworthy that pramipexole, a drug used in Parkinson's disease, also upregulates Bcl-2 in several brain areas, and has been shown to exert antidepressant effects in a double-blind, placebo-controlled trial in patients with bipolar II depression (Zarate *et al*, 2004b). While the DA agonistic effects of pramipexole may clearly also contribute to its purported antidepressant effects, its robust neurotrophic effects suggest that it may have broader utility as an antidepressant potentiator.

Phosphodiesterase Inhibitors (Major Depressive Disorder)

As seen in Figure 1 (pathway a), one approach to enhance the activity of CREB is to use an inhibitor of phosphodiesterase (PDE), the enzyme responsible for the breakdown of cAMP. Indeed, PDE4A and PDE4B may be relevant targets for development of agents that possess antidepressant effects either as monotherapy or in combination with agents that increase intrasynaptic monoamine levels, due to the possible synergism of effects on the cAMP cascade. The idea that PDE inhibitors may have potential antidepressant activity is not a new one, and was initially proposed by Wachtel in the early 1980s (Wachtel and Schneider, 1986). In the 1980s and early 1990s, a number of open-label and controlled clinical trials demonstrated that rolipram, a specific inhibitor of the high-affinity cAMP PDE4, may have antidepressant efficacy in depressed patients (reviewed in Manji *et al*, 2003). In addition, there is some evidence that rolipram may have a faster onset of response compared with standard antidepressants. Despite these data, the potential use of rolipram for depression was limited because of side effects such as nausea and emesis. Second-generation compounds with markedly improved tolerability are being developed (Dyke and Montana, 2002; Huang *et al*, 2001), and it is anticipated that the availability of CNS-penetrant PDE4 inhibitors may lead to the development of a novel class of antidepressants.

Glycogen Synthase Kinase-3 (Bipolar Disorder and Major Depression)

Glycogen synthase kinase-3 (GSK-3) is a ubiquitous, constitutively active, multi-substrate serine/threonine kinase that regulates, and is regulated by, numerous diverse signaling pathways (eg, the Wnt pathway, PI3K pathway, protein kinase A, protein kinase C, among many others; Doble and Woodgett, 2003; see Figure 2). Initial interest in GSK-3 as a therapeutic target for mood disorders arose from the seminal observations that lithium directly inhibited the enzyme (Klein and Melton, 1996; Figure 1, pathway j, while more recent data have highlighted the important role of GSK-3 regulation in the pathophysiology of mood disorders (see O'Brien and Klein, 2007; Gould and Manji, 2005; Gould *et al*, 2006 and references therein). Major findings relevant to both pathophysiology and potential therapeutic mechanisms of action include:

(i) GSK-3 phosphorylation is markedly regulated by agents that increase 5-HT transmission such as d-fenfluramine, fluoxetine, and imipramine such that inhibitory control of GSK-3 might occur in mood disorders marked by 5-HT dysregulation (Li *et al*, 2004).
(ii) GSK-3 is a major regulator of apoptosis and cellular plasticity/resilience (Crowder and Freeman, 2000; Liu *et al*, 2004; Franco *et al*, 2004; Zhao *et al*, 2007). Generally, increased activity of GSK-3 is proapoptotic,

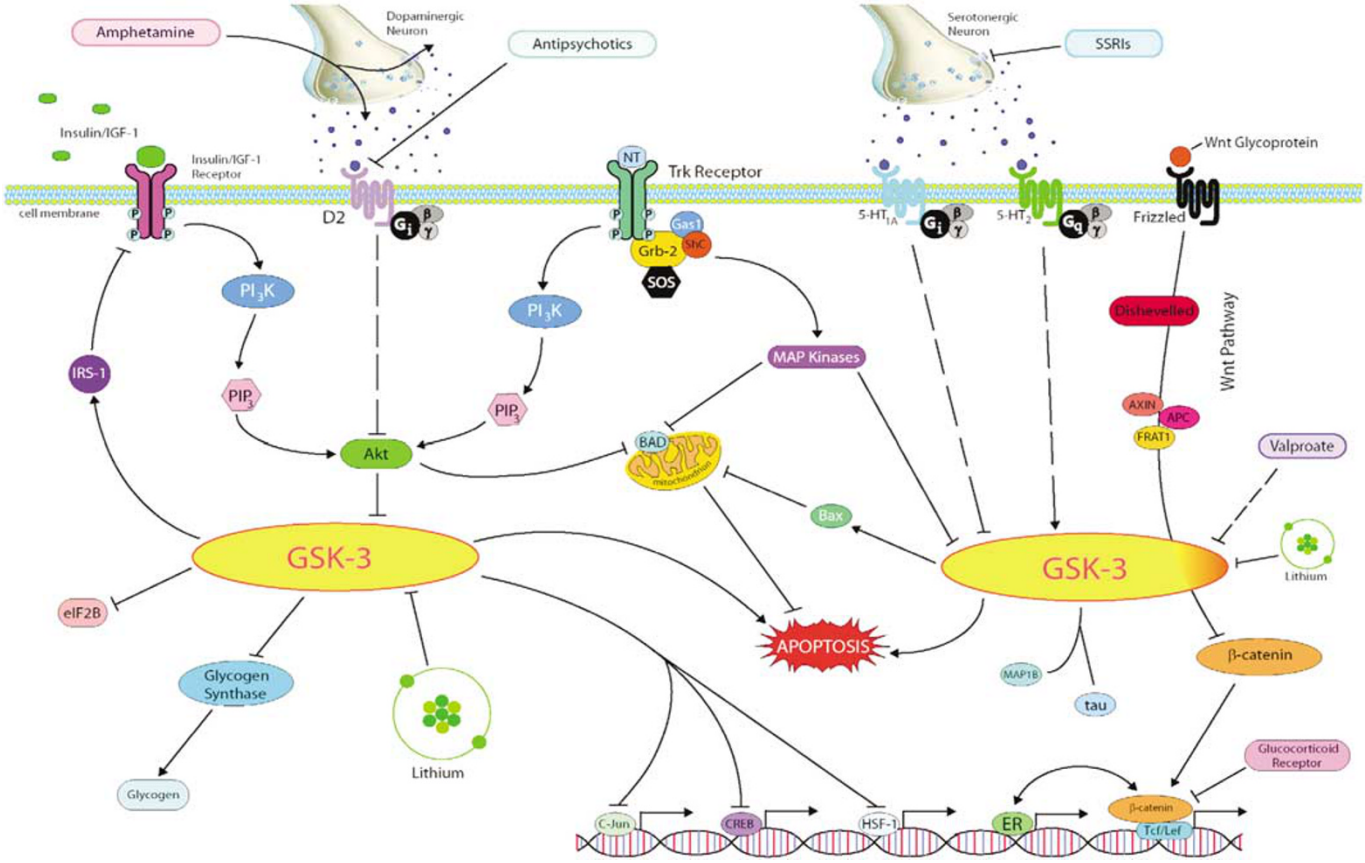

Figure 2 GSK-3 and intracellular signaling. GSK-3 regulates diverse signaling pathways in the cell. These include insulin/insulin-like growth factor (IGF-1) signaling, neurotrophic factor signaling, and Wnt signaling. Insulin signaling through its tyrosine receptor kinase (Trk) receptor activates PI3K-mediated signaling, resulting in inhibition of GSK-3. Inhibition of GSK-3 activates glycogen synthase and eukaryotic initiation factor 2B (eIF2B), while inhibiting insulin receptor substrate-1 (IRS-1, an inhibitor of the insulin receptor). Insulin is generally thought to have minimal effects on CNS neurons; however, IGF-1 interacting with its cognate receptor appears to have similar functions. Neurotrophins (NT) act through Trk receptors A, B, and C to activate PI3K, AKT, and inhibit GSK-3. Many effectors have been implicated in GSK-3's neurotrophic effects, including transcription factors (eg, heat-shock factor-1 (HSF-1), C-Jun, and CREB) and, recently, the proapoptotic Bcl-2 family member BAX. In the Wnt-signaling pathway, secreted Wnt glycoproteins interact with the frizzled family of receptors and, through disheveled-mediated signaling, inhibit GSK-3. Stability of this process requires the scaffolding proteins AXIN and adenomatous polyposis coli (APC). Normally active GSK-3 phosphorylates β-catenin, leading to its ubiquitin-dependent degradation. However, when GSK-3 is inhibited in the Wnt pathway, β-catenin is not degraded, allowing for its interaction with T cell-specific transcription factor (TCF) to act as a transcription factor. β-Catenin activity is modulated by the intracellular estrogen receptor (ER), which also affects transcription of an independent set of genes. As shown in the figure and described in the text, medications useful for the treatment of mood disorders have both direct and indirect effects on GSK-3, and GSK-3-regulated cell signaling pathways. This includes direct effects of lithium and indirect effects of antipsychotics, amphetamine, and selective 5-HT SSRIs. These distinct pathways have convergent effects on cellular processes such as bioenergetics (energy metabolism), neuroplasticity, neurogenesis, resilience, and survival. Thus, our hypothesis is that lithium (and other medications) may act by enhancing these processes through inhibition of GSK-3. G_i refers to G_i/G_o; G_q refers to G_q/G_{11}. Modified and reproduced with permission from Gould and Manji (2005).

whereas inhibiting GSK-3 attenuates or prevents apoptosis (see Gould *et al*, 2006 for review).

(iii) GSK-3 has a major effect on regulating the circadian period in diverse species, an effect it shares with lithium (Gould *et al*, 2004b). Notably, treatment strategies are being developed derived from a chrono-biological model of bipolar disorder (McClung, 2007) based on evidence that the central transcriptional activator of molecular rhythms, CLOCK, may play an important role in the DA system for mood regulation (Roybal *et al*, 2007).

(iv) Recent animal behavioral data (from pharmacologic and genetic models) have shown that manipulation of the GSK-3-signaling cascade produces both anti-depressant and antimanic effects in models of depression or mania. Two separate GSK-3 inhibitors (AR-A014418; Gould *et al*, 2004a and L803-mts; Kaidanovich-Beilin *et al*, 2004) were found to reduce immobility in the forced swim test and attenuate amphetamine-induced hyperactivity. Animals lacking one copy of the GSK-3β gene demonstrate specific behavioral responses to lithium and other GSK-3 inhibitors (Beaulieu *et al*, 2004; O'Brien *et al*, 2004), while transgenic overexpression of GSK was associated with increased activity (Prickaerts *et al*, 2006). This is one of the few manipulations that have been shown to exert both antidepressant and antimanic effects, with two caveats. First, it is not unanimously accepted that amphetamine-induced hyperactivity is a valid model of manic behavior. Second, there is evidence that rolipram (discussed above) also decreases methamphetamine-induced hyperlocomotion (Siuciak *et al*, 2007).

(v) An increase in GSK-3β activity was observed recently in patients with major depression in a postmortem study (Karege *et al*, 2007), and response to lithium augmentation in major depression was associated with the GSK-3β −50T/C single-nucleotide polymorphism (Adli *et al*, 2007).

In view of their potential therapeutic effects not only in bipolar disorder, but also in Alzheimer's disease (Huang and Klein, 2006) and diabetes (Henriksen and Dokken, 2006), it is not surprising that specific, brain-penetrant GSK-3 inhibitors are in development by numerous pharmaceutical companies. GSK-3 phosphorylates and inhibits glycogen synthase, a downstream effector of insulin action, and overactivity of GSK-3 is associated with insulin resistance of skeletal muscle glucose transport (Schloesser *et al*, 2008); accordingly, GSK-3 inhibitors have been tested in prediabetic and type 2 diabetes rodent models (Henriksen and Dokken, 2006). Unless side effects prove to be prohibitive, GSK-3 inhibitors may thus represent a completely novel class of treatment for severe mood disorders, germane to both disease pathophysiology as well as to understanding the mechanism of action of existing treatments (Gould and Manji, 2005; Gould *et al*, 2006).

Protein Kinase C-Signaling Cascade (Bipolar Disorder)

PKC is a shared biochemical target for the actions of chronic lithium and valproate. PKC is highly enriched in the brain, where it plays a major role in regulating both pre- and postsynaptic aspects of neurotransmission. PKC is now known to exist as a family of closely related subspecies, has a heterogeneous distribution in brain (with particularly high levels in presynaptic nerve terminals), and plays a major role in the regulation of neuronal excitability, neurotransmitter release, and long-term alterations in gene expression and plasticity (Manji and Lenox, 1999). A considerable amount of biochemical data support the potential involvement of PKC in the pathophysiology and treatment of bipolar disorder. Evidence supporting this are changes in PKC and its substrates in bipolar patients, and changes in PKC-signaling pathways after treatment with lithium or valproate (Manji and Lenox, 1999). It is noteworthy that psychostimulants, which are capable of triggering manic episodes in susceptible individuals, and induce manic-like behaviors in rodents, are known to activate PKC. Thus, the evidence suggests that two structurally dissimilar antimanic agents—lithium and valproate—attenuate PKC function in a therapeutically relevant time frame, while pro-manic psychostimulants activate PKC. These data suggest that PKC modulation plays a critical role in the treatment of mania. Birnbaum *et al* (2004) demonstrated that excessive activation of PKC dramatically impaired the cognitive functions of the prefrontal cortex, exposure to stress-activated PKC, and resulted in prefrontal dysfunction, and inhibition of PKC (including indirectly with mood stabilizers) protected cognitive function. Pharmacological inhibition of PKC results in many behavioral changes similar to the ones induced by mood stabilizers. These include attenuation of hyperactivity, risk-taking behavior, and hedonic drive; notably, PKC inhibitors attenuate these important aspects of the manic-like syndrome in rodents (Einat and Manji, 2006; Einat *et al*, 2007). Importantly, recent preclinical studies have specifically investigated the antimanic effects of tamoxifen *per se* (since this is the only CNS-penetrant PKC inhibitor available for humans). These studies showed that tamoxifen significantly reduced amphetamine-induced hyperactivity and risk-taking behavior (Einat *et al*, 2007). Notably, a recent whole-genome association study of BPD has further implicated this pathway. Of the risk genes identified, the one demonstrating by far the strongest association with BPD was diacylglycerol kinase, an immediate regulator of PKC (Baum *et al*, 2007). These findings led to a single-blind clinical trial investigating possible antimanic properties of the PKC inhibitor tamoxifen (Bebchuk *et al*, 2000). While best known for its anti-estrogen properties, tamoxifen is also a potent PKC inhibitor at high concentrations. Initial results are encouraging, finding that tamoxifen treatment resulted in a significant decrease in manic symptoms (Bebchuk *et al*, 2000). Larger double-blind, placebo-controlled studies of tamoxifen conducted at NIMH have shown that tamoxifen indeed possesses robust antimanic effects. Subjects on tamoxifen showed significant improvement in mania compared with placebo as early as 5 days, and the effect size for the drug difference was very large after 3 weeks (Zarate *et al*, 2007b). PKC has multiple isoforms and PKC-mediated cellular processes are tissue- and isoform specific. This has allowed the modulation of function of individual isozymes; thus, compounds with isozyme selectivity may find themselves in the therapeutic armamentarium for bipolar disorder, although to date no such compounds have been tested in bipolar disorder (Zarate *et al*, 2006b).

CONCLUSION

Significant paradigm shifts in the psychopharmacology of mood disorders have not occurred in the past several decades, due to poor understanding of disease pathogenesis, imprecise delineation of phenotypic boundaries, and limitations of animal models (Berton and Nestler, 2006). While serendipity will continue to play a role in drug discovery in psychiatry, advances in animal and human genetics, molecular biology, and brain imaging will likely advance the discovery of biomarkers and identify plausible endophenotypes for subgroups of patients with these illnesses. Drugs used commonly in other medical specialties will continue to be explored in mood disorders, based on molecular understanding of their actions. As a prominent recent example, the commonly used β-lactam class of antibiotics were found to increase glutamate uptake via increased expression of glial glutamate transporter (Glt1), thus providing a novel class of compounds that may act to buffer increased glutamatergic release in stress-related conditions (Rothstein *et al*, 2005).

A major thrust of future drug discovery in mood disorders will continue efforts to identify agents with rapid and sustained onsets of action (such as i.v. ketamine and other NMDA receptor-selective subtype antagonists), thereby minimizing disorder morbidity and mortality in the critical weeks between initial symptom expression and drug efficacy. The development of novel PET radioligands

for neurotransmitter receptors not extensively investigated to date (eg, nicotinic and muscarinic cholinergic systems) will shed light on an older literature suggesting that cholinomimetic drugs (ie, muscarinic agonists, acetylcholinesterase inhibitors) exacerbate depressive signs and symptoms such as dysphoria, psychomotor retardation, impairment of attention and memory, HPA axis hyperactivity, and sleep EEG abnormalities (Bertrand, 2005). In a proof-of-concept study, an older antimuscarinic drug, scopolamine (4 μg/kg), was observed to produce potent reductions in depressive severity compared with placebo, with rapid, robust antidepressant responses achieved in 18 patients with unipolar or bipolar depression (Furey and Drevets, 2006).

Finally, while drug discovery efforts have generally focused on specific neurotransmitter receptors or transporters as the target of intervention, there are many additional areas (eg, trafficking proteins, immune modulators) that have not been considered due to space limitations. Next-generation drugs, in addition to treating core symptoms of mood disorders, might be able to target additional important components of these conditions such as enhancing cognition (eg AMPA receptor potentiators), preventing or reversing epigenetic factors that may have long-term negative impact on the course of the illness (eg, histone deacetylase inhibitors), or reducing medical comorbidities such as diabetes (eg, GSK-inhibitors).

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DISCLOSURE/CONFLICT OF INTEREST

Dr Mathew has received compensation over the last three years from AstraZeneca, Cephalon Inc., Pfizer Pharmaceuticals, and Takeda Industries. He has received research grant support from Alexza Pharmaceuticals, Novartis, and Predix Pharmaceuticals. Dr Mathew and Charney have been named as inventors on a use-patent of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and received approval from the Food and Drug Administration (FDA) for this indication, Drs Mathew and Charney could benefit financially.

Dr Manji: A patent application for the use of ketamine in depression has been submitted listing Dr Manji among the inventors. Dr Manji has assigned his rights on the patent to the US government.

Dr Charney has received compensation over the last three years from AstraZeneca, Bristol-Myers Squibb Company, Cyberonics, Forest Laboratories Inc., GeneLogic Inc., Institute of Medicine, Neuroscience Education Institute, Novartis Pharmaceuticals Corporation, Organon International Inc., and Quintiles Inc.

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