Atypical Antipsychotics in Bipolar Depression: Potential Mechanisms of Action

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“Conventional” antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), bupropion, or serotonin-norepinephrine reuptake inhibitors, are not recommended as monotherapy for bipolar depression. Although they are likely to provide effective symptom relief in combination with mood stabilizers, the risk of precipitating a switch to mania often complicates their use even as combination therapy. Recently, 2 psychotropic medications approved for treating acute mania, olanzapine and quetiapine, have also been shown to possess antidepressant activity without destabilizing mood and, as such, are potential mood stabilizers. This article aims to review the mechanism of action of conventional antidepressants and newer agents that are effective in the treatment of bipolar depression. A number of mechanisms have been postulated to play a role in the effective treatment of bipolar depression, including targets as diverse as serotonin (5-HT), norepinephrine, dopamine, γ-aminobutyric acid (GABA), glutamate, and various second messenger signaling pathways. A review of the data reveals an important point of commonality among the antidepressant treatments, olanzapine, and quetiapine. Antidepressant treatments, such as norepinephrine reuptake inhibitors, SSRIs, and electroconvulsive therapy, induce a reduction of 5-HT_{2A} receptors. Both olanzapine and quetiapine not only are antagonists at this receptor but also induce downregulation of 5-HT_{2A} receptors. It is possible that the antidepressant efficacy of these agents is mediated by this receptor, while the additional benefit of olanzapine and quetiapine over unimodal antidepressant treatments, in terms of stabilizing mood, may be provided by their concomitant dopamine D_{2} antagonism. Further studies should be conducted to examine these hypotheses.

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The newer antidepressants are viewed as less likely to destabilize the overall course of illness by causing patients to switch into mania from the depressed phase. Although the data are limited for the efficacy of a combination treatment, it is now common practice to use newer antidepressants in combination with mood stabilizers to treat more severe episodes of acute bipolar depression, and such practice is endorsed by current guidelines. Interestingly, some recent studies show that newer antidepressants, used in combination with lithium or valproate, have a differential propensity for manic switch. For example, venlafaxine is more likely to induce a manic switch than paroxetine, sertraline, or bupropion, and desipramine is associated with higher switch rates than bupropion.

More recently, 2 atypical antipsychotics, olanzapine and quetiapine, have been shown to be effective in bipolar depression in large, randomized, controlled studies (described in detail elsewhere in this supplement). The incidence of treatment-emergent mania in these studies was similar to placebo (olanzapine: 5.7%, olanzapine-fluoxetine: 6.4%, placebo: 6.7%; quetiapine 300 mg/day: 3.9%, quetiapine 600 mg/day: 2.2%, placebo: 3.9%), demonstrating that atypical antipsychotics possess antidepressant properties without destabilizing mood.

Olanzapine and quetiapine are reported to have affinity to several receptors in the brain: serotonin 5-HT1A and 5-HT2, dopamine D1 and D2, histamine H1, α1- and α2-adrenergic, and muscarinic M1 receptors (quetiapine has negligible affinity whereas olanzapine has appreciable affinity at the M1 receptors). Currently it is unclear which of these receptor-binding properties of olanzapine and quetiapine underlie their antidepressant effects. To date, other atypical antipsychotics, such as clozapine, zotepine, aripiprazole, risperidone, and ziprasidone, have not been examined for their efficacy in treating acute bipolar depression in large, randomized, double-blind, placebo-controlled trials. However, preliminary data from small, open-label trials indicate efficacy.

In light of the recent findings of efficacy in bipolar depression with olanzapine and quetiapine and the evidence that they do not destabilize mood, it is of interest to explore which of their multiple receptor mechanisms confer antidepressant and mood-stabilizing properties for these agents. In this article, we will briefly review the neurobiology of depression and the prevailing theories regarding the mechanisms of action of antidepressant medications. The aim is to examine commonalities and differences between the known actions of olanzapine, quetiapine (as these have demonstrated efficacy in bipolar depression), and the more “conventional” antidepressants, such as the SSRIs, SNRIs, and other newer unimodal antidepressant medications. Where possible, evidence from bipolar depression will be discussed, but given that more data are available in patients with major unipolar depression than bipolar depression, reference to key findings from unipolar depression will also be included.

**NEUROBIOLOGY OF BIPOLAR DEPRESSION/Mechanisms of Action of Antidepressant Treatments**

Monoamines (i.e., serotonin, norepinephrine, dopamine) and their receptors, γ-aminobutyric acid (GABA), glutamate, and various second messenger signaling pathways have all been implicated in the neurobiology of bipolar disorder. Much of the evidence for the role of these systems in depression has evolved based on the presumed mechanisms of action of effective therapeutic agents. For example, the amine hypothesis of depression is based on the finding that several antidepressants acutely elevate monoamine (serotonin, norepinephrine, dopamine) levels and drugs that deplete these neurotransmitters can exacerbate depression.

**Serotonin**

A rapidly growing body of data indicates that dysfunction in serotonergic activity may be involved in the pathophysiology of depression. However, the precise role of the serotonin system in depressive symptomatology is unclear. Similarly, the exact mechanism by which SSRIs exert their therapeutic effects is unknown. Several mechanisms have been proposed, including blockade of the 5-HT transporter with consequent increase in synaptic 5-HT levels, down-regulation of presynaptic and up-regulation of postsynaptic 5-HT1A receptors, and down-regulation of 5-HT2A receptors.

There is some evidence that absolute levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are reduced in the cerebrospinal fluid (CSF) of patients with bipolar depression, as revealed by probencid-induced accumulation studies and in postmortem brains of those with bipolar disorder. In addition, some studies show that activity of the 5-HT transporter is reduced in platelets of patients with bipolar depression. Although the affinity differs, all SSRIs, including citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, selectively bind to the 5-HT transporter and block reuptake of 5-HT from the synapse into the presynaptic nerve terminal, thereby raising synaptic 5-HT concentrations with consequent activation of one or more types of 5-HT receptors.

The elevation in 5-HT levels by SSRIs activates not only postsynaptic 5-HT1A receptors but also presynaptic somatodendritic receptors, which reduce the firing activity of 5-HT neurons with consequent reduction in 5-HT levels. Activation of the presynaptic 5-HT1A receptors has been hypothesized to underlie the reason for the latency in onset of action of SSRIs, as it takes up to 2 weeks for these receptors to become desensitized. Some evidence for this hypothesis comes from clinical studies that...
have shown faster onset of action of SSRIs when a β-adrenergic/5-HT1A receptor antagonist, pindolol, was coadministered with SSRI treatment. However, concurrent activation of postsynaptic 5-HT1A receptors has also been shown to occur with fluoxetine.

Several positron emission tomography (PET) studies have shown alterations in 5-HT1A and 5-HT2A receptor binding in patients with depression. Multiple brain regions have shown a decrease in 5-HT1A receptor binding, including frontal, temporal, and limbic cortical regions in unmedicated as well as medicated patients with depression, and reductions in cortical 5-HT2A receptor binding have been found to persist following recovery from a depressive episode even after antidepressant discontinuation. These data indicate that reduction in cortical 5-HT1A receptor binding may be a trait marker that confers vulnerability to depression.

PET studies have also reported reductions in brain 5-HT2A receptor binding in widespread cortical brain regions of antidepressant-free patients. It has been postulated that the reduction in 5-HT2A receptors seen in patients with depression at baseline represents an adaptive mechanism, whereby some patients auto–down-regulate their brain 5-HT2A receptors to achieve relief from a depressive episode. Indeed, there is some evidence that down-regulation of the 5-HT2A receptors may play a role in therapeutic effects of some antidepressant treatments. Initial preclinical studies showed that 5-HT2A receptor–mediated behavior was reduced following 14 days of antidepressant medication, which led to the theory that such reduction is a mediator of antidepressant activity. Clinical evidence for the role of the 5-HT2A receptors in antidepressant mechanism of action comes from imaging studies showing reduced densities of 5-HT2A receptors following treatment with paroxetine, desipramine, nefazodone, or electroconvulsive therapy (ECT).

Thus, the mechanism of action of antidepressants encompasses a number of interactions with the serotonin system, such as increasing synaptic 5-HT levels via blockade of the 5-HT transporter, down-regulation of presynaptic and activation of postsynaptic 5-HT1A receptors, or down-regulation of 5-HT2A receptors.

Norepinephrine

Norepinephrine was originally proposed as the major neurotransmitter involved in both depression and mania in patients with bipolar disorder. Studies in patients with unipolar depression have shown changes in adrenergic receptor density and function that strongly implicate central noradrenergic dysfunction in the neurobiology of depression. Furthermore, reduced levels of norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in urine of patients with unipolar or bipolar depression, as well as reduced norepinephrine and its metabolite levels in postmortem brain samples of patients with bipolar disorder, are consistent with decreased noradrenergic function in bipolar depression.

If noradrenergic system function is decreased in depression, strategies that enhance noradrenergic transmission either through an increase in synaptic norepinephrine levels or functional responsiveness of adrenergic receptors should be effective in relieving depressive symptoms. Indeed, unimodal antidepressants target norepinephrine at several levels to exert their therapeutic effects. For instance, desipramine, reboxetine, venlafaxine, and duloxetine elevate synaptic norepinephrine levels through reuptake inhibition and are effective in treating depressive symptoms. Further, there is some evidence that the functional responsiveness of the α2-adrenergic receptors increases following administration of reboxetine, a selective norepinephrine reuptake inhibitor. Antidepressants have also been shown to target the α2-adrenergic autoreceptors, with agents such as mirtazapine potently antagonizing central α2-adrenergic autoreceptors and heteroreceptors, thus enhancing noradrenergic transmission.

Dopamine

There is some evidence that depression in bipolar disorder may be due to low dopamine levels. Of the major dopaminergic pathways, the mesocorticolimbic system, which innervates limbic structures such as the nucleus accumbens, ventral hippocampus, and prefrontal cortex, is involved in a variety of functions related to motivation and reward that may be implicated in depression. In contrast, the nigrostriatal dopamine pathway is involved in motor functions, while the tuberoinfundibular pathway plays a role in endocrine functions. Consistent with this, region-specific reductions in D2 binding—in the frontal cortex but not the striatum—have been shown in patients with bipolar disorder compared with control subjects. The role of dopamine in bipolar depression is further supported by findings of low levels of homovanillic acid (HVA, dopamine metabolite) in the CSF of patients with major depression.

Inhibition of dopamine reuptake has been postulated as a target of antidepressant action. Drugs that inhibit dopamine uptake, such as maprotiline and bupropion, are effective antidepressants. Furthermore, some of the SSRIs, such as sertraline, have been shown to inhibit dopamine reuptake, while other SSRIs, such as fluoxetine, have been shown to increase extracellular dopamine in the rat prefrontal cortex. Similarly, venlafaxine also inhibits dopamine reuptake, although to a lesser extent than either serotonin or norepinephrine reuptake. This mixed action of venlafaxine makes it a potentially useful agent in the treatment of patients with depression who are refractory to agents that affect only one of those monoamine systems. Further, antidepressant properties of dopamine receptor agonists, such as bromocriptine and pramipexole, in patients with bipolar depression also support a role for dopamine in mechanisms of antidepressant treatments.
A study by Lammers and colleagues\textsuperscript{52} showed that several types of antidepressants (amitriptyline, desipramine, imipramine, and tranylcypromine) significantly increased D\textsubscript{4} receptor messenger ribonucleic acid (mRNA) expression in the shell of the nucleus accumbens after 21 days of treatment, while fluoxetine significantly increased D\textsubscript{4} receptor mRNA after a 42-day treatment. These authors suggested that the up-regulation of the D\textsubscript{4} pathway, involved in reward and motivation, may represent a common neurobiological mechanism of antidepressant action.\textsuperscript{52} The D\textsubscript{4} receptor has also been implicated in the mechanism of antidepressant action. Twelve patients with unipolar depression who were treated with paroxetine showed significantly lower levels of D\textsubscript{4} dopamine receptor mRNA compared with 10 healthy controls. Following an 8-week treatment with paroxetine, the D\textsubscript{4} dopamine receptor mRNA levels had returned to control levels.\textsuperscript{53} Few studies examined the effects of antidepressants on the D\textsubscript{4} dopamine receptor. For instance, antidepressants such as imipramine have been reported to have activating effects on the dopamine D\textsubscript{4} receptor\textsuperscript{54,55}; however, preclinical studies have shown no effect of fluoxetine, desipramine, or tranylcypromine administration on D\textsubscript{4} dopamine receptor mRNA expression in subregions of the nucleus accumbens and striatum.\textsuperscript{56}

### GABA

Another system hypothesized to play a role in depression is the GABA system. GABA is one of the most abundant neurotransmitters in the brain, and recent postmortem studies have implicated this system in the biology of bipolar disorder.\textsuperscript{57} The integrity of the GABAergic system was estimated using the synthetic enzymes glutamic acid decarboxylase (GAD)-65 and GAD-67 as markers; reduced levels of both enzymes were identified in the cerebellum of patients with bipolar disorder.\textsuperscript{57}

### Neuronal Pathway Interconnections and Neurotransmitter Interactions

Serotonergic, noradrenergic, and dopaminergic transmitter systems all interact with each other, and they all affect the glutamatergic neurons. Some researchers have suggested that an interaction between some or all of these pathways may mediate expression of symptoms in unipolar and bipolar depression.\textsuperscript{58} Also of particular note is the functional interplay between serotonin and dopamine systems. The 5-HT\textsubscript{2A} receptors on presynaptic dopaminergic neurons have a tonic inhibitory effect on dopamine release, whereas blockade of these presynaptic 5-HT\textsubscript{2A} receptors by 5-HT\textsubscript{2A} antagonists increases dopamine levels.

### Second Messenger Signaling Pathways

In addition to the neurotransmitters discussed above, other target molecules postulated to play a role in the neurobiology of bipolar depression and therapeutic effects of antidepressant treatments include G protein subunits, protein kinase A (PKA)/protein kinase C (PKC), or second messengers, such as mitogen-activated protein kinase (MAPK) (Figure 1).\textsuperscript{59} The effects of antidepressants on second messenger signaling pathways, rather than their primary effects on receptors, may underlie the antidepressant efficacy of some agents. Norepinephrine, dopamine, and most 5-HT receptors are G protein coupled. Antidepressants, by acting on these G protein–coupled receptors, activate second messenger systems, such as adenyl cyclase, and increase the concentration of cyclic adenosine monophosphate (cAMP). Up-regulation of cAMP levels leads to activation of cAMP-dependent PKA, which activates the phosphorylation of the transcription factor cAMP response element binding protein (CREB). CREB activation may be mediated by Ca\textsuperscript{2+}-dependent protein kinases (e.g., Ca\textsuperscript{2+}/calmodulin-dependent protein kinase [CaMK] and PKC), and studies have shown activation of cAMP and calcium-calmodulin–dependent kinases following antidepressant treatment of patients with either unipolar depression or bipolar disorder.\textsuperscript{60} Some antidepressants (desipramine, tranylcypromine, fluoxetine) have been shown to induce an increased phosphorylation of CREB in brain areas such as the amygdala and hippocampus. This is important, as phosphorylation is a prerequisite for CREB function. Brain-derived neurotrophic factor (BDNF) is a downstream target of the cAMP signaling pathway. Increased postmortem expression of BDNF has been demonstrated in the hippocampus of patients who were treated with antidepressants but not in those who were antidepressant-free.\textsuperscript{61}

### MECHANISM OF ACTION OF ATYPICAL ANTIPISYCHOTICS IN BIPOLAR DEPRESSION

Among the atypical antipsychotics, currently only olanzapine and quetiapine have been shown to provide significantly greater efficacy than placebo in the treatment of bipolar depression.\textsuperscript{62,63}

### Serotonin-Mediated Effects

Olanzapine and quetiapine both affect serotonin neurotransmission, potentially contributing to their antidepressant effects and reflecting similarities between these and the newer antidepressants. Both are antagonists at the 5-HT\textsubscript{2A} receptor. As previously stated, PET studies indicate that SSRIs, norepinephrine reuptake inhibitors, noradrenergic and specific serotoninergic antidepressants, and ECT down-regulate brain 5-HT\textsubscript{2A} receptors. Quetiapine has a higher affinity for serotoninergic receptors than dopaminergic receptors.\textsuperscript{64} A consistently higher degree of 5-HT\textsubscript{2A} receptor occupancy than dopamine D\textsubscript{4} receptor occupancy with quetiapine has been observed in PET studies (74% versus 41%, respectively, at 750 mg/day).\textsuperscript{65} Also, the duration of 5-HT occupancy with quetiapine significantly
outlasts the duration of D₂ occupancy. Animal studies have shown that atypical antipsychotics that block 5-HT₂₅ receptors down-regulate brain 5-HT₂₅ receptors.⁶⁶ Thus, down-regulation of this serotonin receptor subtype—5-HT₂₅—seems to represent a strong point of commonality among olanzapine, quetiapine, and the antidepressant treatments, such as paroxetine, nefazodone, desipramine, and ECT.

Interestingly, olanzapine and quetiapine also have partial agonistic activity on the serotonin system, increasing activity at 5-HT₁₅ receptors. There is some regional specificity in their partial agonist action at the 5-HT₁₅ receptors as it occurs in the prefrontal cortex but not the nucleus accumbens.⁶⁷ In the prefrontal cortex, 5-HT₁₅ receptor stimulation increases dopamine release. Thus, olanzapine and quetiapine appear to selectively increase dopamine levels in the prefrontal cortex via a 5-HT₁₅-related mechanism.⁶⁷ Both olanzapine and quetiapine appear to have affinity to the 5-HT₆ receptor,⁶⁸ although the contribution of this receptor for antidepressant effects remains unknown.

Norepinephrine-Mediated Effects
Olanzapine exhibits potent antagonistic activity at α₁-adrenergic receptors in vitro.⁶⁸ Animal studies have shown that olanzapine alone and the combination of olanzapine and fluoxetine lead to a substantial increase in the firing of locus ceruleus neurons with consequent elevation in norepinephrine release in prefrontal cortex.⁶⁹ Similarly, quetiapine alone has been reported to increase norepinephrine levels in the prefrontal cortex.⁷⁰ The potential involvement of the α₂-adrenergic receptors has also been investigated, with quetiapine showing greater affinity for the α₂₅ receptor subtype compared with other atypical antipsychotics.⁷¹

Dopamine-Mediated Effects
Olanzapine and quetiapine increase dopamine release in the prefrontal cortex.,⁷⁰,⁷² most likely through their effects on 5-HT₁₅ and 5-HT₂₅ receptors. 5-HT₂₅ receptors are present on presynaptic dopamine neurons, and stimulation of these heteroreceptors inhibits dopamine release whereas blockade leads to increased dopamine release. Since atypical antipsychotics block 5-HT₂₅ receptors, they are expected to increase dopamine levels in the prefrontal cortex. Further, animal studies have shown that atypical antipsychotics increased dopamine release by stimulating 5-HT₁₅ receptors in the prefrontal cortex.⁶⁷ Quetiapine and olanzapine are both dopamine D₂ antagonists. However, it has been shown that quetiapine binds more loosely than olanzapine to the dopamine D₂ receptor.⁷³ It is postulated that rapid dissociation from the D₂...
receptor underlies the “atypicality” of the mechanism of action of atypical antipsychotic agents. Atypicality is defined as a lower propensity for extrapyramidal symptoms, although sometimes other definitions are used. Rapid dissociation could also help explain the human PET studies showing that the occupation of D2 receptors by quetiapine is transiently high at 2 to 3 hours and disappears 24 hours later. Transient D2 receptor occupancy may account for less dysphoria with quetiapine compared with other, more potent D2 blockers. Indeed, in clinical trials looking at patients with bipolar I depression, quetiapine has shown a larger effect size (relative improvement versus placebo) than olanzapine (1.09 for quetiapine 600 mg/day and 0.91 for quetiapine 300 mg/day vs. 0.32 for olanzapine alone and 0.68 for olanzapine in combination with fluoxetine). In further support of this hypothesis, clinical trials comparing olanzapine with haloperidol have shown that haloperidol is less effective at improving depressive symptoms and induces a faster rate of switching to depression when administered for acute mania, a possible consequence of the higher and prolonged occupancy of D2 receptors observed with haloperidol. The dopamine antagonism of olanzapine and quetiapine may be responsible for antimanic effects but also, in concert with 5-HT2A antagonism, may account for mood-stabilizing properties of these drugs. Many unimodal antidepressants that do not antagonize D2 receptors have been reported to induce manic symptoms. As excessive dopamine may underlie the expression of manic symptoms, it may be advantageous that olanzapine and quetiapine concomitantly block dopamine D2 receptors and dampen dopamine signaling in areas that are rich in D2 receptors, such as the limbic system and basal ganglia, thus preventing the dopamine-induced switching to hypomania. Alternative mechanisms, such as D2 partial agonism, may in the future prove useful in providing a similar mood-stabilizing effect. However, the clinical effects of such agents have yet to be demonstrated in bipolar depression.

Alternative Mechanisms of Action

An effective agent in bipolar depression may act through multiple mechanisms. Although this has not been the subject of many studies to date, it will undoubtedly be explored in future research. Although the exact involvement of components such as second messenger signaling pathways in the neurobiology of bipolar disorder is unclear, it is of interest to note some commonality among effects of SSRIs, olanzapine, and quetiapine on such pathways. Quetiapine has activity at targets as diverse as neurotransmitters, glutamate receptors, and BDNF. It is not thought that agents such as olanzapine or quetiapine can directly inhibit glutamate receptors, but quetiapine exposure has been associated with altered expression of the glutamate receptor subunits. Preclinical studies have shown reduced glutamate release in the prefrontal cortex following acute or chronic SSRI administration. Another point of commonality among these agents is their effect on expression of immediate-early genes. Elevations of c-Fos in limbic areas have also been demonstrated with fluoxetine, olanzapine, and quetiapine.

CONCLUSION

Multiple neurotransmitter targets appear to mediate the mechanism of action of agents used to treat bipolar depression. Reviewing the receptor targets of those agents that have demonstrated efficacy in bipolar depression reveals certain points of commonality (Table 1; Figure 2). Although the SSRIs predominantly act by increasing serotonin levels, they also appear to down-regulate 5-HT2A receptors in order to mediate effective antidepressant actions. Similarly, agents such as olanzapine and quetiapine antagonize 5-HT2A receptors, in addition to their dopamine D2 receptor blockade. It would seem probable that a regionally selective balance between the dopamine and serotonin systems is required to stabilize mood, and it would be predicted that other agents with similar pharmacologic profiles would also provide similar clinical efficacy. Since excessive dopamine in the mesolimbic system may underlie the expression of manic symptoms, it may be advantageous that olanzapine and quetiapine concomitantly dampen dopamine signaling in mesolimbic pathways, thus preventing the dopamine-induced switching to hypomania.
that can occur with unimodal antidepressants. It appears that olanzapine and quetiapine—through their neurotransmitter antagonism of both 5-HT2A and D receptors—represent effective mood-stabilizing agents.

**Drug names:** aripiprazole (Abilify), bromocriptine (Parlodel and others), buproprion (Wellbutrin and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nefazodone (Serzone and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbax), paroxetine (Paxil, Pexeva, and others), pinadolol (Visken and others), pramipexole (Mirapex), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor), ziprasidone (Geodon).

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