Atypical antipsychotics in major depressive disorder

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The antipsychotics are used among pharmacological treatment of depression. Atypical antipsychotics have been used as monotherapy or adjunctively with antidepressants to treat depressive disorders with or without psychotic symptoms. The antidepressant effect of atypical antipsychotics involves regulation of monoamine, glutamate, gamma-aminobutyric acid, cortisol, and neurotrophic factors. To date, the United States Food and Drug Administration has approved aripiprazole and quetiapine slow-release tablets as adjunctive treatment for depressive disorders, and the combination of olanzapine and fluoxetine for the treatment of treatment-resistant depression. When using atypical antipsychotics in the treatment of depressed patients, clinicians need to monitor patients for the emergence of adverse effects, including hyperglycemia, weight gain, cholesterol levels, and extrapyramidal symptoms. These agents are effective for depression only at subantipsychotic doses. Receptor profiles predict that all second-generation antipsychotics will have anxiolytic effects as subantipsychotic doses but that all will be dysphorogenic at full antipsychotic doses (i.e. produce a depression-like clinical picture). The antidepressant effect appears to be unique to some agents. Also, despite the availability of a large number of antidepressants of different classes, a significant portion of patients do not achieve remission, and treatment resistance is common. This paper reviews the antipsychotics that are effective for the treatment of depressive disorders, and the pharmacological mechanisms of antipsychotics in the treatment of depressive disorders.

Keywords:
antidepressants, antipsychotics, second-generation antipsychotics

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Introduction

Some second-generation antipsychotics (SGAs), for example, aripiprazole, quetiapine XR, olanzapine, and brexpiprazole, had a formal United States Food and Drug Administration (USFDA) approval as an augmentation therapy to antidepressants in the treatment of major depressive disorder (MDD) (Wang *et al.*, 2016). Among them, olanzapine was approved for the treatment of treatment-resistant depression (TRD), which is defined as MDD patients who did not respond to two separate trials of two or more than two antidepressants after an appropriate duration and dose, as a combined agent with fluoxetine (Wang *et al.*, 2016). Brexpiprazole had received FDA approval not only for schizophrenia, but also for the treatment of MDD as an adjunctive therapy to antidepressants in July 2015, which is the biggest change since 2013. In addition, FDA approved lurasidone for bipolar depression, cariprazine for the acute treatment of manic or mixed episodes associated with bipolar I disorder (Corponi *et al.*, 2019).

This paper reviews the antipsychotics that are effective for the treatment of certain depressive disorders, the pharmacological mechanisms of antipsychotics in the treatment of depressive disorders, and adverse reactions when using antipsychotics in the treatment of depressive disorders.

There has been substantial progress in the search for further treatment strategies for treatment-resistant MDD (TRD): psychotropics augmentation other than antidepressants, and antidepressant switches and combinations, regardless of antidepressant classes. Among them, augmentation treatment with atypical antipsychotic agents has been recognized as an important option. Moreover, SGAs have been an area of focus after successful augmentation using risperidone to selective serotonin-reuptake inhibitors (SSRIs) was found in 1991 (Ostroff and Nelson, 1999). Thereafter, three SGAs, including olanzapine (2007), quetiapine-extended release (2007), and aripiprazole (2009) were approved by the USFDA as an augmentation therapy to antidepressants for treating MDD (Han *et al.*, 2013).

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Table 1 Phases of recovery with expected psychosocial symptoms and suggested treatments

Phases	Expected symptoms	Recommended treatments
Admission	Anxiety, terror	Psychological support
	Pain	Reassurance
	Sadness, grief	Relaxation techniques
		Antianxiety medication
		Analgesic medication
Critical care phase	as at admission plus.	Continued psychological support
	Acute stress disorder	Antianxiety medication
		Analgesics
		Medication targeting acute stress disorder symptoms
In-hospital recovery	Increased pain with exercise anger, rage grief-depressive episodes, and rapid emotional shifting	Psychotherapy (cognitive–behavioral and family therapy)
		Targeted administration of analgesics
		Pharmacological treatment of anxiety and depression
Rehabilitation and reintegration	Adjustment difficulties	Psychotherapy (cognitive–behavioral and family therapy, social skills)
	Posttraumatic stress disorder	Medication targeting posttraumatic stress disorder
	Anxiety (including phobic response)	Anxiolytics tapered off over time
	Depression	Antidepressant medication

The general information on SGA, including the current market situation for MDD, is summarized in Tables 1 and 2.

Table 2 Assessment tools

Anxiety	Depression anxiety stress (DAS) scale DAS scale
Depression	DAS scale
PTSD	Impact of event scale revised
Acute stress	DAS scale

Antipsychotics are effective for the treatment of certain depressive disorders

USFDA has approved the use of aripiprazole (5–10 mg/d, maximum dosage 15 mg/d) as an adjunctive medication in the treatment of depressive disorders. Combined treatment with olanzapine and fluoxetine has been approved by the USFDA for the treatment of TRD (olanzapine 5–20 mg/d, fluoxetine 20–50 mg/d) (Chen *et al.*, 2011; Maher and Theodore, 2012). Slow-release quetiapine (150–300 mg/d) has also been approved by the USFDA as an adjunctive treatment for depressive disorders; this is the only atypical antipsychotic approved in Europe as an adjunctive treatment for depression, and in Australia, it has been approved both as an auxiliary treatment and as a primary treatment for depression.

Meta-analyses have assessed the effectiveness and side effects associated with the use of various atypical antipsychotics as adjunctive or primary treatment for depressive disorders and dysthymia (Komossa *et al.*, 2010). Slow-release quetiapine: pooled results from seven double-blind randomized control trails (n=3414) found improved depressive symptoms when used alone or when used jointly with antidepressants, but it also had a clear sedative effect. Olanzapine: pooled results from seven double-blind randomized control trails (n=1754) found that adjunctive treatment with olanzapine improved patient adherence to treatment, but it was not associated with improved treatment effects and it was associated with weight gain and increased prolactin levels. Aripiprazole (three studies, n=1092) and risperidone (four studies, n=637): when used as adjunctive treatment to antidepressants, both medications improved the outcomes, but they were associated with weight gain and increased prolactin levels (Komossa *et al.*, 2010). No significant differences have been found in the antidepressant effects of the different atypical antipsychotic medications assessed (Chen *et al.*, 2011).

Some studies have also shown benefits of antipsychotic treatment during the maintenance phase of treatment for depression. A 52-week follow-up study reported that relapses were fewer among individuals with depressive disorders who received monotherapy with slow-release quetiapine (50–300 mg/d) during the maintenance phase of treatment than in those given placebos (Sagud *et al.*, 2011). Another study found that the relapses were delayed among those who received adjunctive treatment with risperidone or amisulpride compared with those who received placebos as adjunctive treatment (Chen *et al.*, 2011).

Pharmacological mechanisms of antipsychotics in the treatment of depressive disorders

The antidepressant effect of typical antipsychotics is presumed to be related to the inhibition of D2/D3 receptors on the dopamine (DA) pathway in the prefrontal cortex, which increases the DA level in the prefrontal cortex. The antidepressant effects of atypical antipsychotics include rapid disengagement of DA receptors, reduced activation of DA receptors, reduced activation of 5-hydroxytryptamine 1A (5-HT1A) receptors, inhibition of 5-HT2A/2C receptors, inhibition of α2 receptors, the blockage of the norepinephrine (NE) transporter, the regulation of the glutamate (GA) or the gamma-aminobutyric acid (GABA) system, a decrease in cortisol levels, and an increase in brain-derived neurotrophic factor (BDNF) levels (Wang and Si, 2013).

Dopamine

The effect of atypical antipsychotics on mood is related to the rapid release of DA from the receptor and the consequent reduced activation of DA receptors. In untreated schizophrenia, the occurrence of positive symptoms is a result of increased output of DA in the midbrain limbic system; the occurrence of cognitive impairment and negative symptoms is a result of decreased output of DA in the cerebral cortical pathways to the dorsal prefrontal cortex; and the occurrence of mood and negative symptoms is a result of decreased output of DA in the cerebral cortical pathways to the ventral prefrontal cortex. In theory, the D2 receptors need to be blocked in order to reduce the DA function in the cerebral cortical pathways and to prevent the exacerbation of mood, cognition, and negative symptoms following rapid release of DA from the receptor. Rapid release translates into low potency. Low-potency medications (i.e. those that require a high dosage to achieve a treatment effect such as clozapine and quetiapine) can be released faster from the D2 receptors compared with high-potency medications (i.e. those for which a low dosage achieves a treatment effect such as risperidone), and medium-potency medications (such as olanzapine), which have an intermediate disengagement speed (Si *et al.*, 2011).

Partial activation of DA receptors reduces DA output in the midbrain limbic system, which leads to fewer positive symptoms, but is not enough to influence senses of pleasure and satisfaction. Since the DA output in the cerebral cortical pathways may be too low, partial DA activists actually increase DA release in this area, which leads to improved cognition, mood, and negative symptoms (Si et al., 2011). Partial DA activists include aripiprazole, amisulpride, and sulpiride (for amisulpride and sulpride, the clinical indicators of partial DA activation are more evident at low dosages) (Si *et al.*, 2011).

There is a wide variation in the treatment effects of antipsychotics. At low dosages, many nondopaminergic antipsychotics have the same mechanism of action as antidepressants: increasing DA transmission in the prefrontal cortex. Lavergne and Jay (2010) hypothesized that depressive disorders are a result of 'synaptic depression' caused by decreased DA transmission and elevated D1 receptor functioning in the prefrontal cortex, changes that can be corrected by increasing DA transmission (Filip and Bader, 2009). Increased functioning of DA can improve synaptic plasticity and neuroregeneration, but there is a U-shaped dose–response relationship between DA activity and synaptic plasticity (Lavergne and Jay, 2010). The interaction between DA and GA is via the D1 receptor subtype and the N-methyl-D-aspartate (NMDA) receptor, so BDNF may play a regulatory role in this process (Lavergne and Jay, 2010).

5-hydroxytryptamine

Different atypical antipsychotic medications have very different binding affinity for different types of 5-HT receptors (De Sousa and Kurvey, 2012). These differences in binding capacity are often more apparent when combined with antidepressants (De Sousa and Kurvey, 2012).

The activation of the 5-HT1A receptor leads to the closure of the 5-HT neuron impulse, decreased electroactivities and release of 5-HT, decreased postsynaptic concentration of NE and 5-HT, and reduced inhibition of NE and DA (Si *et al.*, 2011). Postsynaptic 5-HT1A receptors inhibit the release of GA from neurons in the cortical pyramid and regulate the metabolism of hormones that influences mood, anxiety, and cognition. When 5-HT1A is activated by 5-HT, signals are delivered by the second messenger cyclic adenosine monophosphate and promote gene expression. This increase in gene expression can help the regulation of neurotransmitters and neurotrophic factors which, in turn, help the alleviation of depressive symptoms (Si *et al.*, 2011). In support of this explanation for the role of 5-HT1A receptors, a study of 5-HT1A receptor gene-knockout mice reported increased anxiety-related behaviors, an anti-depression-like phenotype, and impaired cognition (Filip and Bader, 2009). Moreover, the effect of the partial 5-HT1A receptor activators (such as buspirone) is delayed, similar to antidepressants, which suggests

that the treatment effect is related to upstream or downstream adaptation rather than to acute changes in these receptors (Si *et al.*, 2011).

The isoreceptor function of the 5-HT2A receptor is through the expression at DA, GABA, GA, and Ach neurons on the dendrite of the cell. In vivo microdialysis found that activation of the 5-HT2A receptor may boost the release of GA and GABA and inhibit the release of DA and NE (Filip and Bader, 2009). Contrary to the 5-HT1A receptor, when 5-HT2A is activated, the delivery is blocked at the second messenger system cyclic adenosine monophosphate and, thus, inhibits gene expression. In mice, the destruction of the entire 5-HT2A receptor messenger system reduced the inhibition of conflict anxiety and did not influence behaviors related to fear and depression; selective recovery of the cortex 5-HT2A receptor signals restored the conflict anxiety behavior (Filip and Bader, 2009).

5-HT2C receptors are located in GABA, GA, and DA neurons. They function as cellular dendrite isoreceptors (Filip and Bader, 2009). *In vivo* neurochemical studies found that the activation of 5-HT2C receptors can inhibit the release of DA and NE in the cortex (Filip and Bader, 2009). A study found that 5-HT2C receptor-mutated mice did not show obvious anxiety induced by 5-HT2C receptor stimulants (Filip and Bader, 2009), which suggest that these receptors influence emotions and behavior.

The inhibition of 5-HT2C receptors is also related to extended slow-wave sleep and the increase of sleep efficiency – which are associated with the core symptoms of depression. Among individuals with depressive disorders, there is less slow-wave sleep, a shorter latency period of REM sleep, shorter sustained sleep time, a longer latency period for sleep initiation, longer awake time, more frequent REM sleep, and more θ and δ waves in the sleep EEG (Begić *et al.*, 2009). SSRIs usually lead to increased 5-HT levels between synapses inducing both treatment effects and unintended side effects (Filip and Bader, 2009), including sleep disorders related to the stimulation of 5-HT2C receptors. Low dosages of atypical antipsychotics can inhibit 5-HT2C receptors and, thus, decrease the occurrence and severity of these anti-depressant-induced sleep problems, enhancing the treatment effects of SSRI antidepressants (Si *et al.*, 2011). A single 5-mg dose of olanzapine can extend slow-wave sleep, total sleep time, and sleep efficiency, and reduce time awake (Gimenez *et al.*, 2007); a single 1-mg dose risperidone can reduce REM sleep (Gimenez *et al.*, 2007). The effect of extended slow-wave sleep of olanzapine and ziprasidone is related to 5-HT2C receptor inhibition (Gimenez *et al.*, 2007). The binding ability of quetiapine to 5-HT2C receptors is low, so it does not influence slow-wave sleep (Gedge *et al.*, 2010), but daily treatment with 155 mg of quetiapine for 2–4 days has been shown to decrease REM sleep, possibly due to its high binding ability with H1 receptors (Jensen *et al.*, 2008).

Experimental data suggest that the 5-HT7 receptor is the key mediator for the antidepressant effect of aripiprazole (Abbas *et al.*, 2009). The combination of SSRIs and 5-HT7 receptor antagonists can increase the treatment effects of SSRIs (Hedlund, 2009). Animal studies have also found that 5-HT6 receptor antagonists can enhance the effects of antidepressants (Wesolowska, 2010).

Norepinephrine

NE is located in many brain areas. It is the main monoamine neurotransmitter that regulates arousal and stress reactions. Reduced activities in the prefrontal cortex regulated by NE may be related to decline in cognitive functioning (e.g. attention) and motivation. Since noradrenergic descending fibers from the nucleus coeruleus also go to brain areas that regulate motor functioning (i.e. the striatum and cerebellum), NE may also be related to the regulation of physical fatigue. N-desalkylquetiapine, the metabolite of quetiapine, can block the NE transporter and promote the delivery of NE; the binding of quetiapine to the NE transporter is almost negligible (Sagud *et al.*, 2011).

NE and NE neurons as well as the α2 receptor on the presynaptic membrane of the 5-HT neuron can block the release of NE and 5-HT. Antagonists of the α2 receptor can relieve this inhibition and increase the release of 5-HT and NE, producing an antidepressant effect. Additionally, the α1 receptor on the postsynaptic membrane of the NE and 5-HT neurons can enhance the release of 5-HT. Thus, when NE inhibition is blocked, the α1 receptor is activated, which leads to a magnified release of 5-HT (Wang and Si, 2013). Preclinical neurological data show that the antidepressant mechanism of risperidone is due to the inhibition of the α2 receptor (Dhir and Kulkarni, 2008); some researchers believe the antidepressant effect of quetiapine is also moderated by the inhibition of the α2 receptor.

SSRIs increase the transmission of 5-HT in the cerebrum and nucleus ceruleus, and thus, decrease the discharge of NE neurons. Atypical antipsychotics increase the discharge of NE neurons via the inhibition of 5-HT2A, α2, or NE transporters. This may be the reason that SGA are effective among depressed patients who get limited benefit from SSRI treatment (Blier and Szabo, 2005).

Glutamate

GA is the main neurotransmitter stimulant in the central nervous system. The physiological functions of GA are usually moderated via nonionic mechanisms such as NMDA, ?-amino-hydroxy methyl oxazole propionic acid, kainic acid receptor, and metabolic GA receptor (Garakani *et al.*, 2013). Several reports have suggested the key role of GA in the neurobiology and treatment of depressive disorders. Abnormal GA functioning has been found in patients with depressive disorders and some GA-related medications have shown some antidepressant effects (Tokita *et al.*, 2012). Several metabolic GA receptors [e.g. 9-aminomethyl-9,10-dihydroanthracene and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)] and the GA transporter have been associated with the development and treatment of depressive disorders (Tokita *et al.*, 2012).

Studies have found that quetiapine can decrease mRNA expression of the NR-1 and NR-2C subtypes of the NMDA receptor in the septal nuclei (Porcelli *et al.*, 2011). Quetiapine can also increase the expression of the G luR-B and G luR-C subtypes of the AMPA receptor in the hippocampus (Porcelli *et al.*, 2011). Some researchers hypothesize that quetiapine can normalize GA neurotransmission and decrease the risk of overstimulation by changing the activities of the GA receptors (Blier and Szabo, 2005).

Gamma-aminobutyric acid

Preclinical and clinical studies found that inhibition of the GABA system is related to the pathophysiology of depression. The regulation of extracellular concentrations of NE and DA in the prefrontal cortex by the administration of quetiapine is regulated by NMDA that is moderated by AMPA and GABA (Porcelli *et al.*, 2011). Joint use of fluvoxamine and haloperidol led to changes in GABA receptors and signal-delivery systems in some brain regions in rats; this change was not observed when fluvoxamine or haloperidol were used alone (Silver *et al.*, 2011). Similar observations have been reported among patients with schizophrenia; some studies suggest that combined treatment may lead to a better improvement of negative symptoms (Silver *et al.*, 2011). There has been no study on this topic among patients with depressive disorders.

Hypothalamic–pituitary–adrenal axis

Mood disorders are related to changes in the stress-response system. Convincing evidence has been found for increased cortisol levels among patients with depressive disorders (Stetler and Miller, 2011). Unlike haloperidol, low-dose quetiapine and olanzapine can decrease cortisol levels among healthy volunteers (Cohrs *et al.*, 2006). However, there has been no study about the changes in cortisol levels after the use of antipsychotics among patients with depressive disorders (Sagud *et al.*, 2011), so it is unclear whether or not the hypothalamic–pituitary–adrenal axis plays a role in the antidepressant effect of antipsychotic medications (Sagud *et al.*, 2011).

Brain-derived neurotrophic factor

Preclinical and clinical studies have found that the increase of neurotrophic factors, especially BDNF, is a common characteristic in the mechanisms of action of antidepressant medications. A meta-analysis summarizing 11 studies found decreased BDNF levels in untreated depression and a return of BDNF levels to the normal after antidepressant treatment (Sen *et al.*, 2008). These findings have led some researchers to propose using BDNF concentration as a biomarker for disease severity and treatment effects (Sen *et al.*, 2008). After the use of SGA such as olanzapine, plasma BDNF levels increase (González-Pinto *et al.*, 2010). Moreover, one relatively small study found that the increase in BDNF levels of depressed patients treated with a variety of antipsychotics and antidepressants was greater in patients considered responsive to the combined treatment (Yoshimura *et al.*, 2010). This suggestive study needs to be repeated with a larger sample that would allow differentiation of the results for different combinations of medications.

Adverse reactions when using antipsychotics in the treatment of depressive disorders

Due attention should be paid to the potential side effects of antipsychotic medications when considering adjunctive treatment in patients with depressive disorders. These side effects include the metabolic syndrome (e.g. poor regulation of the metabolism of sugar and fats), extrapyramidal symptom (EPS), high prolactin, sedation, abnormal liver function, and cardiac irregularities (Sagud *et al.*, 2011). The doses of antipsychotic medications used as adjunctive treatment in depression are usually lower than when used as the primary treatment in schizophrenia and

bipolar disorder, so the prevalence and severity of these side effects is usually lower (Corponi *et al.*, 2019; Chen *et al.*, 2011), but clinicians must be vigilant about these adverse reactions, particularly in elderly patients.

In the mid-1980s, two studies observed a high prevalence of tardive dyskinesia after long-term use of typical antipsychotics in individuals with mood disorders (Baldessarini, 1988; Keck *et al.*, 2000). Subsequent studies (Keck *et al.*, 2000; Vacheron-Trystram *et al.*, 2004) reported that the prevalence of tardive dyskinesia in patients with mood disorders who were treated with antipsychotic medication ranged from 9 to 64%. Among these studies, only one study included patients with schizophrenia (Keck *et al.*, 2000); this study reported that the occurrence of tardive dyskinesia was higher among mood-disorder patients (42%) than in patients with schizophrenia (25%).

In general, the occurrence of EPS is lower for atypical antipsychotics compared with typical antipsychotics (except for aripiprazole). With the exceptions of risperidone and paliperidone, the influence of atypical antipsychotics on the level of prolactin is also smaller than that of typical antipsychotics.

For patients with TRD who require long-term medication, the advantage of adjunctive treatment with antipsychotics can be considerable, but chronic use of these medications, even at relatively low doses, can lead to increases in blood lipids, triglycerides, and glucose, resulting in weight gain and an increased risk of type II diabetes. These risks are greatest with clozapine and olanzapine; moderate with paliperidone, risperidone, and quetiapine; and small with aripiprazole and ziprasidone. Except for clozapine, the antidepressant treatment effects of different atypical antipsychotics are similar, so the side-effect profile should be the deciding factor in the choice of antipsychotic medication (Hasnain *et al.*, 2012). Clinicians need to consider the patient's age, weight, BMI, medical history, and family history of diabetes and cardiovascular diseases when weighing the potential risks of different antipsychotics (Zuddas *et al.*, 2011). When using atypical antipsychotics as adjunctive treatment for depressed patients, clinicians should follow the guidance about monitoring and screening of the American Diabetes Association (Morrato *et al.*, 2009) and should counsel patients about diet, exercise, and a healthy lifestyle. When lifestyle interventions fail to prevent weight gain in young patients using low-dose atypical antipsychotics, metformin can be considered if other SGA are not suitable (Hasnain *et al.*, 2012).

In older patients, the side effects of SGA include increased mortality [number needed to harm (NNH)=87], stroke (risperidone NNH=53), EPS (olanzapine NNH=10, risperidone NNH=20), and urinary-system symptoms (NNH=16–36) (Maher and Theodore, 2012). Clinicians need to carefully weigh the potential benefits and potential risks of long-term adjunctive treatment of elderly depressed patients with antipsychotic medications.

Conclusion

There is considerable evidence on the efficacy of some SGAs as an adjunction to antidepressants in MDD. Brexpiprazole, aripiprazole, quetiapine XR, and olanzapine plus fluoxetine are approved by FDA. Quetiapine XR was proven effective also as a monotherapy. While their mechanism is not completely understood, antagonism of serotonergic and noradrenergic receptors, blockade of monoamine transporters, effects on sleep, decrease in cortisol levels, and increase in neurotrophic growth factors seem to be involved. Antipsychotics should be given at the lowest effective dose in patients to MDD, and patients need close monitoring for additional adverse events.

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Conflicts of interest

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