ANTIPSYCHOTICS AS ANTIDEPRESSANTS: WHAT IS THE MECHANISM?

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INTRODUCTION

Antidepressants are first-line treatment for patients with major depressive disorder (MDD). The mechanism of action of antidepressants is still not completely understood. While most antidepressants directly inhibit the reuptake of at least one monoamine neurotransmitter in the brain (serotonin, dopamine or noradrenalin), or block their degradation, mirtazapine, tianeptine and agomelatine, which are also similarly effective as other antidepressant drugs, do not act this way. Despite the availability of large number of antidepressants of different classes, significant portion of patients do not achieve remission, (Rush et al. 2006), and treatment-resistance is common (Nemeroff 2007).

EFFICACY OF ANTIPSYCHOTICS IN MDD

There is persuasive evidence for the antidepressant efficacy of some SGAs in clinical trials (Chen et al. 2011), as well as for the increase of their prescription in the treatment of patients with MDD (Konstantinidis et al. 2011). Moreover, the use of SGAs in MDD is anticipated to grow and continue to be one of the leading augmentation strategies (Chen et al. 2011). In the last three years, some antipsychotics have gained FDA approval for add-on treatment in MDD, as presented in table 1.

Table 1. Antipsychotics approved for the treatment of MDD

Antipsychotic	Indication	Doses for MDD	Doses for schizophrenia
Aripiprazole	Adjunct to antidepressants for MDD	5-10 mg/day, Maximum dose: 15 mg/day	10-30 mg/day
Quetiapine XR	Adjunct to antidepressants for MDD	150-300 mg/day	400-800 mg/day
Olanzapine	Treatment-resistant depression (TRD), in combination with fluoxetine	Olanzapine 5-20 mg/day Fluoxetine 20-50 mg/day	10-20 mg/day

Adapted from: Olanzapine prescribing information 2009, Aripiprazole prescribing information, 2008, Quetiapine XR prescribing information, 2011

The following SGAs have been investigated in double-blind trials in patients with MDD: Amisulpride, aripiprazole, olanzapine, risperidone and quetiapine XR. Those studies have been carried out in two ways: as monotherapy or as addition to treatment with anti-depressant. Among antipsychotics, quetiapine XR has been the most extensively studied, followed by olanzapine, aripiprazole and risperidone (Komossa et al. 2010). Double-blind trials investigating quetiapine efficacy in improving symptoms in depression included 3414 participants (Komossa et al. 2010). In addition to efficacy in treating acute symptoms of depression, quetiapine XR in dose of 50-300 mg daily, was found to be effective as monotherapy in maintenance treatment, compared to placebo, in a follow-up period of 52 weeks (Liebowitz et al. 2010). Our group reported clinical improvement in TRD after quetiapine was added to antidepressants (Sagud et al. 2006).

There is some evidence of ziprasidone efficacy as add-on treatment in patients with treatment-resistant major depression (TRD) (Papakostas et al. 2002; Dunner et al. 2007). In an open, randomized study, patients with TRD the addition of 160 mg daily of ziprasidone to high dose of sertraline, had greater effect size and greater CGI-S improvement compared to patients who received 80 mg ziprasidone daily (Dunner et al. 2007). The study had small sample size and high attrition rate (Dunner et al. 2007). In a retrospective chart review, add-on treatment of ziprasidone to anti-depressants was effective in some patients with TRD, but not different from other atypical antipsychotics (Barbee et al. 2004). At present, there are no data for the efficacy of paliperidone and sertindole in major depression, and there are no randomized clinical trials for clozapine.

Studies of SGAs in major depression included heterogeneous groups of patients with varying degrees of treatment resistance (Chen et al. 2011). The doses of some antipsychotics in those trials were lower than average recommended clinical doses in the treatment of schizophrenia. Quetiapine XR dose was 150 and 300mg respectively (Weisler et al. 2009, Liebowitz et al. 2010), and amisulpride dose was as low as 50 mg daily (Cassano et al. 2002).

MECHANISM OF ANTIDEPRESSANT EFFICACY OF ANTIPSYCHOTICS

All known antipsychotics are blockers of dopamine D2 receptors, although at different degree. High D2 receptor occupancy was related to increase in negative affect. Increased levels of D2 receptor occupancy for tight dopamine D2 receptor blockers haloperidol and risperidone were associated with negative emotional experience, in contrast with loose D2 receptor blocker olanzapine, based on theoretical prediction of D2 occupancy (Lataster et al. 2010).

Given those effects of high D2 receptor occupancy, antidepressant efficacy might be expected in antipsychotics with low D2 receptor occupancy, such as quetiapine, clozapine or olanzapine, partial D2 receptor agonists such as aripiprazole (Blier & Blondieau 2011), or low-dose of antipsychotics with otherwise high D2 occupancy, such as ziprasidone, amisulpride or risperidone.

There are several mechanisms which might, at least in part, explain antidepressive efficacy of antipsychotics. Those are: Blockade of neurotransmitter receptors other than dopamine, blockade of monoamine transporters, effects on sleep, decrease in cortisol levels and increase in neurotrophic growth factors.

Table 2. Effects of interacting with different neurotransmitter receptors by antipsychotics

Mechanism	Proposed effect	Antipsychotics that might be involved
Serotonin 5HT1A receptor agonism	Increase in dopamine release in frontal cortex	Aripiprazole, N-desalkylquetiapine, Ziprasidone
Serotonin 5HT2A receptor antagonism	Increase in dopamine release in frontal cortex	Clozapine, N-desalkylquetiapine, olanzapine, risperidone, sertindole, ziprasidone
Serotonin 5HT2c receptor antagonism	Increase in dopamine and noradrenalin release in frontal cortex	Clozapine, Olanzapine, Ziprasidone
Adrenergic α-2 receptor antagonism	Increase of dopamine, serotonin and noradrenalin release in frontal cortex	Clozapine, Quetiapine, Risperidone
Serotonin 5HT7 receptor antagonism	Increase of serotonin in prefrontal cortex (PFC)	Amisulpride, Aripiprazole, Clozapine, N-desalkyl-quetiapine Risperidone, Sertindole, Olanzapine
Serotonin 5HT6 receptor antagonism	Increase of dopamine, noradrenalin, glutamate and acetylcholine* in frontal cortex and hippocampus	Clozapine, Olanzapine, Sertindole

*While increase of acetylcholine is important for enhancing cognitive function, it is unknown whether it affects depression

Affinity on monoamine receptors other than dopamine

Many of non-dopaminergic properties occur at low doses of antipsychotics (Schwartz & Stahl 2011), leading to a shared common mechanism with antidepressants, such as increase of dopamine neurotransmission in prefrontal cortex (PFC). Clinical depression is proposed to be the state of „synaptic depression", due to decreased dopaminergic neurotransmission via D1 receptors in the PFC (Lavergne & Jay 2010). There is a great heterogeneity in binding to those receptors among antipsychotics. Preclinical studies suggest that effects on different receptors might contribute to increase of dopamine in PFC and hippocampus. Those data are presented in table 2 (Schechter et al. 1990, Wesolowska 2010, Schmidt et al. 2002, Abbas et al. 2009, Kuroki et al. 2009, Schechter et al. 2008, Mørk et al. 2009, Minzenberg & Yoon 2011, Millan et al. 2003, Dhir & Kulkarni 2008, Jensen et al. 2008, Bymaster et al. 2009).

Those assumptions are derived mostly from preclinical studies. It appears that those effects are more pronounced when antipsychotics are combined with antidepressants. Each antipsychotic has a unique combination of affinities toward different receptors. Amisulpride is a potent 5HT7 receptor antagonist. Preclinical data suggest that 5HT7 receptors are critical mediators of its antidepressant response (Abbas et al. 2009), and that the addition of 5HT7 blocking agents to SSRI augments their efficacy (Hedlund 2009). Preclinical data further report that α-2 blockade is responsible for risperidone potentiation of antidepressant effects of fluoxetine or venlafaxine (Dhir & Kulkarni 2008). The review of animal studies of behavioral models of depression suggests that the administration of 5HT6 receptor antagonists potentiates the affects of antidepressants (Wesolowska 2010). In a double blind study, olanzapine and fluoxetine combination was more effective that each agent alone, in patients with TRD (Thase et al. 2007). Antidepressant activity of quetiapine is proposed to be mediated via α-2 blockade, which, in turn, increases noradrenergic neurotransmission. Similar receptor profiles of quetiapine and mirtazapine suggest the mechanism that makes

quetiapine effective as monotherapy in depression (Blier & Blondieau 2011).

Blockade of monoamine transporters

Further mechanism for antidepressant effects of antipsychotics is the ability to increase serotonin or noradrenalin levels. Unlike any other SGAs, ziprasidone was reported to block synaptic serotonin, noradrenalin and dopamine reuptake in vitro (Tatsumi et al. 1999; Schmidt et al. 2001). However, it's affinity for serotonin transporter was only moderate compared with those of SSRIs and duloxetine. It remains to be determined whether this moderate affinity is sufficient to affect monoamine transporters in humans.

In addition, quetiapine metabolite, N-desalkylquetiapine, is a potent noradrenalin reuptake inhibitor, while its parent drug quetiapine has negligibly affinity for noradrenergic transporter. Interestingly, in spite of aforementioned noradrenergic activity of quetiapine metabolite, quetiapine combination with venlafaxine in the treatment of major depression was reported (Baune et al. 2007; McIntyre et al. 2007). Moreover, N-desalkylquetiapine is ten fold more potent 5HT1A receptor agonist than quetiapine, as well as more potent serotonin 5HT2A and 5HT7 receptor antagonist, respectively (Jensen et al. 2008). Those properties are supposed to contribute to antidepressant efficacy of quetiapine.

Increase in neurotrophic growth factors

In the treatment of both major depression and schizophrenia, there is a delay in response to drug of at least 2 to 4 weeks. Preclinical and clinical data suggest that increased in brain neurotrophic factors is shared common denominator in the action of antidepressants, with brain-derived neurotrophic growth factor (BDNF) being the most frequently investigated. The meta-analysis of 11 studies revealed both reduced serum BDNF levels in untreated depressed patients (Sen et al. 2008), and their normalization after treatment with antidepressants (Sen et al. 2008). Antidepressants were found to increase BDNF protein expression in rat hippocampus (Musazzi et al. 2009). Withstanding those findings, BDNF level was proposed to be a biomarker of illness and antidepressant response (Sen et al. 2008). Plasma BDNF levels were also reported to be increased after the treatment with atypical antipsychotics, such as olanzapine (González-Pinto et al. 2010). Moreover, it has been reported that plasma BDNF levels in responders were increased 4 weeks after the add-on antipsychotic treatment, compared to non-responders, with a correlation between observed changes in HAM-D scores and plasma BDNF levels (Yoshimura et al. 2010). However, the study included small number of patients with either depression or bipolar disorder in depressed phase, and patients were given different antipsychotics and antidepressants (Yoshimura et al. 2010).

Effects on sleep

The next mechanism of antipsychotics in depression might be their influence on different sleep parameters. Sleep disturbance and dysregulated sleep rhythm are among core symptoms of depression, and could be very disturbing for the patient. Depressed patients were reported to have decreased slow-wave sleep (SWS) (Hubain et al. 1995, Rotenberg et al. 2000) and REM latency (Hubain et al. 1995), as well as shorter sleep duration, increased sleep latency, increased wakefulness (Rotenberg et al. 2000), increased REM density (Gillin et al. 1988) and increased theta and delta EEG rhythms (Begić et al. 2009). Insomnia is frequently reported in patients treated by SSRIs (Ensrud et al. 2006). On the contrary, some antipsychotics were found to have profound impact on sleep, even in low dose. Olanzapine, given in a single dose of 5 mg, was reported to increase SWS, total sleep time and sleep efficiency and decrease wake time (Giménez et al. 2007). In the same study, risperidone after the single 1 mg dose has decreased REM sleep (Giménez et al. 2007). Similarly, olanzapine even after single 2.5 mg dose, as well after repeated treatment, was found to enhance SWS and sleep efficiency in depressed patients resistant to SSRIs (Sharpley et al. 2005). Olanzapine's effect on SWS is believed to be attributed to its 5HT2c binding properties (Sharpley et al. 1994), because olanzapine was reported to be a particularly potent 5HT2c antagonist (Bymaster et al. 1999). Ziprasidone, another potent 5HT2c blocker, was also found to increase the SWS, and sleep efficiency, after very low dose of 40 mg daily (Cohr et al. 2005). On the contrary, quetiapine, which has low 5HT2c affinity, did not affect SWS (Gedge et al. 2010). However, it decreased the percentage of REM sleep, and increased time spent in non-REM sleep, after 2 to 4 days of treatment in the average dose of 155 mg daily (Gedge et al. 2005). Since quetiapine, and particularly its metabolite desalkylquetiapine, have high H1 antagonistic activity (Jensen et al. 2008), improvement of sleep and agitation similar to antihistaminics could be expected (Schwartz & Stein 2011). Those properties could contribute to rapid improvement of depressive symptoms on quetiapine, which is, consistently across studies, observed after one week of treatment (Bauer et al. 2009, Cutler et al. 2009, Bortnick et al. 2011) and as early as on day 4 of treatment (Weisler et al. 2009). Similarly, the combination of olanzapine and fluoxetine had higher efficacy after first week of treatment, compared with nortryptiline (Shelton et al. 2005). Rapid improvement in depressive symptoms appears as an advantage compared to usual onset of improvement on antidepressants after 2 to 4 weeks. In patients with TRD, improvement in depressed mood was preceded by improvement of both sleep and anxiety (Sagud et al. 2006).

Decrease in cortisol levels

There is compelling evidence for the association between depression and increased cortisol levels (Stettler & Miller 2011). While, unlike haloperidol, low-dose quetiapine and olanzapine were reported to decrease cortisol levels in healthy volunteers (Cohrs et al. 2006), there are no reports of their influence, or of any other atypical antipsychotics, on cortisol levels in depressed patients. It remains to be determined whether this mechanism is also involved in the antidepressant activity of antipsychotics.

Some atypical antipsychotics act as antidepressants in lower dose, and as both antipsychotic and antimanic agents in higher dose (Schwartz & Stahl 2011). Therefore, low-dose SGAs have increasingly important role in the treatment of major depressive disorder. In addition, patients who received lower doses of antipsychotics had also lower discontinuation rate from clinical trials, compared to those with higher doses (Chen et al. 2011). The efficacy of SGAs in major depression should be balanced against the potential for adverse effects, such as extrapyramidal symptoms (EPS), hyperglycemia, dyslipidemia, prolactin elevation, sedation and effects on cardiac conduction (Chen et al. 2011, Komossa et al. 2010).

CONCLUSION

There is considerable evidence on efficacy of some SGAs as an adjunction to antidepressants in MDD, and aripiprazole, quetiapine XR and olanzapine plus fluoxetine are yet 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 a lowest effective dose in patients to MDD, and patients need close monitoring for additional adverse events.

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