Review article

An evidence based clinical review on the role of atypical antipsychotics in depression

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Abstract

Today though we have a large number of antidepressants, there are also a large number of patients who do not respond to traditional antidepressant therapy. Various augmentation strategies have been suggested in these cases the foremost being atypical antipsychotic therapy. In fact atypical antipsychotic drugs (aripiprazole and quetiapine) have received US FDA approval as augmenting agents in the treatment of major depression. The present review looks at the various studies of atypical antipsychotics in the management of depression along with efficacy amongst individual drugs. The various mechanisms that may result in antidepressant action by atypical antipsychotics have been discussed along with novel mechanisms that may play a role. The review concludes that atypical antipsychotics have a place in the pharmacotherapy of depression and are useful agents as both augmentation strategies and in the management of treatment resistant depression.

Keywords*: Atypical antipsychotics, Depression.*

Introduction

Antidepressants are always first-line treatments for patients with major depressive disorder (MDD). The mechanismof action of antidepressants is still not completely understood.[1] While most antidepressants inhibitthe reuptake of at least one neurotransmitterin the brain i.e. serotonin, dopamine or noradrenalin, and others block their degradation, we have many newer antidepressants like mirtazapine, tianeptine and agomelatine, which are similarly effective as the others but act via novel mechanisms and receptors. Despite thediverse pharmacology of antidepressants ofdifferent classes, a large proportion of depressed do not achieve remission[2] and treatment resistance is common.[3]

Atypical antipsychotics as antidepressants

There is persuasive evidence for the antidepressantefficacy of some SGAs in certain clinical trials[4]and several studies document an increase of their prescription inthe treatment of depression.[5] Moreover the use of atypical antipsychotics in depression is anticipated to grow and has been one of theleading augmentation strategies in depression.[4] Inthe last few years, some antipsychotics have gained US FDA approval for add-on treatment in major depression. These are olanzapine, quetiapine extended release and aripiprazole. Of these aripiprazole and quetiapine have been approved as an adjunctive therapy in major depression while olanzapine has been approved for treatment resistant depression in combination

with fluoxetine.

Many atypical antipsychotics have been investigated indouble-blind trials in patients with depression. Studies have been reported for amisulpride, aripiprazole, olanzapine, risperidone and quetiapine XR. Most of the studies have been carried out in two ways viz. as monotherapy or as addition to existent treatment with an antidepressant.Among the atypical antipsychotics, quetiapine XR has been the most extensively studied, followed by olanzapine, aripiprazole and risperidone.[6] Double-blind studies investigating quetiapine included nearly 3500 participants.[6] In addition toits efficacy in treating acute symptoms of depression, quetiapine XR in doses of 50-300mg daily, was found tobe as effective as monotherapy in maintenance treatment for depression compared to placebo, in a follow-up period of 52 weeks.[7] Researchers have reported clinicalimprovement in treatment resistant depressive symptoms after quetiapine was added toantidepressants.[8-9]

There is some evidence of the usefulness of ziprasidone as an add-on treatment in patients with treatment-resistantdepression.[10-11] In a recent study,patients with treatment with treatment resistant depression were given 160 mg/day of ziprasidone which was added to a high dose of sertraline. This had greater effectsize and greater improvement scores compared topatients who received 80mg ziprasidone per day. The study had a small sample size and hence cannot be generalized.[11] In another retrospectivechart review, add-on treatment of ziprasidone to antidepressants was effective in some patients with depression,but not in greater efficacy than other atypical antipsychotics.[12] To the best of our knowledge at the time of writing this review, there are no reported trials of the efficacy of paliperidone and sertindole in majordepression. The same holds true for for clozapine.

Most studies of atypical antipsychotics in major depression have includedheterogeneous groups of patients with varying degreesof treatment resistance. Hence meta-analysis of many studies is often difficult.[4]The doses of some of the atypical antipsychotics in those studies are often lower than the recommended clinical doses in the treatment of schizophrenia. Quetiapine XR has been used in doses 150-300mg[13] and amisulpride has been used in doses as low as 50 mg per day.[14]

Postulated antidepressant actions of atypical antipsychotics

All known antipsychotic drugs (typical and atypical) are blockers of dopamine (D2) receptors, although at different degrees. High D2 receptor occupancy has been related to increase in negativeaffect. Increased levels of D2 receptor occupancy fortight dopamine binding and blocking drugs like haloperidol andrisperidone were associated with negative emotionalexperience while a loose D2 receptor blockerolanzapine, based on theoretical prediction of D2occupancy may be associated with less effect on negative affect.[15]

Given those effects of high D2 receptor occupancy,antidepressant efficacy might be expected inantipsychotics with low D2 receptor occupancy, such asquetiapine, clozapine or olanzapine and partial D2 receptoragonists such as aripiprazole.[16] Antidepressant efficacy may also be demonstrated with low-dosages of antipsychotics with otherwise high D2 occupancy such as ziprasidone, amisulpride orrisperidone.[17]

There are several mechanisms which may explain the antidepressant efficacy of antipsychotics.These are the blockade of neurotransmitter receptors other than dopamine i.e. serotonin antagonism, blockade of monoamine transporters, the effects of these

drugs on sleep and decrease in cortisol levels with an increase in neurotrophic growth factors expression.[18]

The emerging of role of serotonin in atypical antipsychotic action

Many of the non-dopaminergic actions of atypical antipsychotics occur at lower dosages.[19] This leads to a shared common mechanism with antidepressants with an increase of dopamine neurotransmissionin prefrontal cortex. Clinical depressionis proposed to be the state of 'synaptic depression' dueto decreased dopaminergic neurotransmission via D1 receptors in this region of the brain.[20] There is agreat heterogeneity in serotonin receptor binding amongst various antipsychotics (Table 1). Preclinical and laboratory based animal studies suggest that the effectson different serotonin receptors might contribute to increase ofdopamine in the prefrontal areas and the hippocampus.[21-23] These effects are often morepronounced when antipsychotics are combined withantidepressants. Each atypical antipsychotic has a uniquecombination of affinities toward different serotonin receptors (Table 1).

Amisulpride is a potent $5HT_7$ receptor antagonist. Laboratory data suggests that $5HT_7$ receptors are criticalmediators of the antidepressant response to aripiprazole.[24]Reports have shown that the addition of $5HT_7$ blocking agents toSSRIs augments their efficacy.[25] (Hedlund 2009). Preclinical neuroscience data further reports that $\alpha_2$adrenergic receptor blockade is responsiblefor the mechanism of action of Risperidone as an antidepressant.[22]

The review of animal studies of behavioural models of depression suggests that the administration of $5HT_6$ receptor antagonists potentiates the effects ofantidepressants.[21] In a double blindstudy, olanzapine and fluoxetine combination was moreeffective that each agent alone, in patients with treatment resistant depression.[26] Antidepressant activity of quetiapine has been proposed to be mediated via α_2 blockade,which in turn, increases noradrenergic neurotransmission.[27]

Further mechanisms for antidepressant effects ofantipsychotics is the ability of these drugs to increase serotonin ornoradrenaline levels. Unlike any other atypical antipsychotic, ziprasidone has been reported to block synaptic serotonin, noradrenaline and dopamine reuptake in vitro.[28] However, it's affinity for the serotonintransporter was only moderate compared with those of SSRIs and duloxetine.[28] In addition, quetiapine metabolite, N-

Table 1 – Serotonin mechanisms of atypical antipsychotic drugs

Serotonin Receptors	Effect on the brain	Atypical antipsychotics involved
$5HT_{1A}$agonism	Frontal dopamine release	Aripiprazole, Quetiapine, Ziprasidone
$5HT_{2A}$ antagonism	Frontal dopamine release	Quetiapine, Olanzapine, Risperidone, Ziprasidone
$5HT_{2C}$ antagonism	Frontal dopamine and norepinephrine release	Olanzapine, Ziprasidone
α_2 adrenergic antagonism	Frontal dopamine and serotonin release	Quetiapine, Risperidone
$5HT_7$ antagonism	Serotonin release in the prefrontal cortex	Amisulpride, Aripiprazole, Risperidone, Olanzapine
$5HT_6$ antagonism	Dopamine, glutamate and acetylcholine release in the frontal cortex and hippocampus	Olanzapine

desalkylquetiapine, is a potent noradrenaline reuptake inhibitor,while quetiapine has negligible affinityfor the noradrenergic transporter. Quetiapine combination with venlafaxine has been however reported efficacious inthe treatment of major depression.[29] Moreover, N-desalkylquetiapineis 10 times a more potent $5HT_{1A}$ receptor agonist as well as a more potentserotonin $5HT_{2A}$ and $5HT_{7}$ receptor antagonist than quetiapine itself.[30] These properties aresupposed to contribute to the antidepressant efficacy ofquetiapine in major depression.

Novel mechanisms of antidepressant action by atypical antipsychotic drugs

In the treatment of major depression there is often a delay in the full clinical response to the drug of atleast 2-3 weeks. Clinical data suggests that increase in various neurotrophic factors is a sharedcommon denominator in the action of antidepressantswith brain-derived neurotrophic growth factor (BDNF)being the most frequently investigated. A meta-analysisof 11 studies revealed both reduced serumBDNF levels in untreated depressed patients and their normalization after treatment with antidepressants.[31] Plasma BDNF levels have also been also reported to be increasedafter treatment with atypical antipsychotics, such asolanzapine.[32] Studies have also shown that plasma BDNF levels inresponders were increased four weeks after the add-onantipsychotic treatment compared to non-responders.[33]

Another postulated mechanism of atypical antipsychotic efficacy in depression is probably their influence on different sleep parameters. Sleep disturbance and dysregulated sleep rhythm areamong core symptoms of depression, with decreased slow-wave sleep (SWS),decreased REMlatency, shorter sleepduration, increased sleep latency, increased wakefulness, increased REM density and increased theta and delta EEG rhythms.[34-35]

Insomnia is a common finding inpatients treated by SSRIs.[36] On thecontrary some of the atypical antipsychotics have been found to have a profound impact on sleep even at low doses. Olanzapine, even in a single dose of 5mg, has been reported to increase total sleep time and sleep efficiency and decrease wake time. In fact olanzapine even after single 2.5 mg dose, as well after repeated treatment, was found to enhance slow wave sleep and sleep efficiency in depressed patients resistant to SSRIs.[37-38]

Ziprasidone which is a potent $5HT_{2C}$ receptor blocker, was also found toincrease the slow wave sleep and sleep efficiency after doses as low as 40 mg daily.[39] Quetiapine does not however affectslow wave sleep due lack of a $5HT_{2C}$ binding but it decreases the percentage of REM sleep and increases the time spent innon-REM sleep, after 2-4 days of treatment in thedose of 50-150 mg daily.[40] Since quetiapine hasa high H_{1} antagonistic activity improvement of sleep and agitation similar to antihistaminics could be expected.[19] The effects of quetiapine on sleep contribute to its rapid improvement of depressive symptoms seen across studies even as early as after one week of treatment.[41-42]

There is strong evidence for the association between depression and increased cortisol levels in blood.[43] Low dose quetiapine and olanzapine were reported todecrease cortisol levels in healthy volunteers there are no reports of their influence or ofany other atypical antipsychotics, on cortisol levels indepressed patients. It remains to be determined whether this mechanism is also involved in the antidepressant activity of antipsychotics.[44]

Conclusion

The efficacy of atypical antipsychotics in

major depression must be balanced against the potential for adverse effects, such as extra-pyramidal symptoms (EPS), hyperglycemia, dyslipidemia and prolactin elevation along with sedation. There is considerable evidence on the efficacy of some atypical antipsychotics as an adjunct to antidepressants in major depressive disorder. While theirmechanism is not completely understood, antagonism of serotonergic and noradrenergic receptors, blockade of monoamine transporters, effects on sleep, decrease incortisol levels and increase in neurotrophic growth factors seem to be involved. Antipsychotics should be given at a lowest effective dose in patients with major depression while all patients need close monitoring for additional adverseevents.

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