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Second Generation Antipsychotics in the Treatment of Major Depression

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Editorial

Although antipsychotics were developed for the treatment of schizophrenia, the newer ones, the second generation antipsychotics (SGAs), are always more often used to treat depressive symptoms particularly when they have not been improved by using antidepressants or other treatments. Depression is a common health problem but many patients, 60-70%; don't get adequate treatment because of antidepressants is ineffective for up to 40% of cases. Several atypical antipsychotics are currently proposed and used in monotherapy or augmentation therapy and add-ons, to treat Major Depression (MD), particularly in the case of "resistant depression". They are aripiprazole, quetiapine, amisulpride, olanzapine, ziprasidone, asenapine, iloperidone, lurasidone, paliperidone, risperidone, brexpiprazole and clozapine. Three, aripiprazole, quetiapine, olanzapine and a combination tablet olanzapine plus the antidepressant fluoxetine are approved by the Food and Drug Administration for this use, but the other antipsychotics are often used "off-label" [1,2].

However, several Authors indicate that antipsychotics are not as effective as augmentation therapy for treating "resistant MD" and are not the best choice for most depressed patients. Other options, such as increasing the dose of the antidepressant or switching to different ones, are at least both effective and safer. Antipsychotics can also cause serious side effects, such as involuntary movements, significant weight gain, and an increased risk of type 2 diabetes, heart disease, and stroke. In addition, they are very expensive [3]. For those reasons, in our opinion, the atypical antipsychotics could not be considered good first choices as antidepressants or as add-ons to antidepressants, especially in the case of overweight, heart disease or diabetes patients. In any case there are persuasive evidences for the antidepressant efficacy of some SGAs in clinical trials, as well as for the increase of their prescription in the treatment of patients with MD. Moreover, the use of SGAs in MDD is anticipated to grow and continue to be one of the leading augmentation strategies.

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 antidepressant [4]. Among antipsychotics, quetiapine XR has been the most extensively studied, followed by olanzapine, aripiprazole and risperidone. Double-blind trials investigating quetiapine efficacy in improving depressive symptoms included more than 3000 participants. 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 [4]. Aripiprazole is approved for the acute and maintenance treatment of manic and mixed episodes associated with bipolar disorder type I (BD) but a meta-analysis supports the usefulness of aripiprazole during all phases of bipolar illness demonstrating its effect also against acute Bipolar Depression [5].

On the other hand, also aripiprazole is an effective augmentation strategy for improving therapeutic response in patients with treatment-resistant MD when administered in combination with standard antidepressant therapy [6,7]. Regarding olanzapine it has demonstrated more efficacy than placebo, and combined olanzapine-fluoxetine has shown more efficacy than olanzapine and placebo in the treatment of bipolar I depression without the risk of developing manic symptoms [8]. Some data seem to suggest that risperidone is beneficial as an augmenting treatment in MD patients who have developed high-risk suicidal ideation during a depressive episode. The antisuicidality effect of risperidone is especially valuable in the acute management of severe depressive symptoms [9] although from a clinical point of view, in our experience, the antidepressant effect of risperidone seems doubtful.

There is some evidence of ziprasidone efficacy as add-on treatment in patients with treatment-resistant MD. These patients have demonstrated greater effect size and greater improvement with the addition of 160 mg daily of ziprasidone to high dose of sertraline compared to patients who received only 80 mg daily of ziprasidone [10]. A new SGA, brexpiprazole, was recently approved by the Food and Drug Administration in July 2015 for the treatment of MDD as an augmentation agent to antidepressants and it has a lower intrinsic activity at the dopamine D₂ receptor and it has an approximately 10-fold higher affinity for serotonin 5-HT_{1A} and 5-HT_{2A} receptors than aripiprazole [11].

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. Moreover studies of SGAs in major depression included heterogeneous groups of patients with varying degrees of treatment resistance. 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 300 mg respectively, and amisulpride dose was as low as 50 mg daily.

All known antipsychotics are blockers of dopamine D₂ receptors, although at different degree. High D₂ receptor occupancy was related to increase in negative affect. Antidepressant efficacy might be expected with antipsychotics with low D₂ receptor occupancy, such as quetiapine or olanzapine, partial D₂ receptor agonists such as aripiprazole, or low-dose of antipsychotics with otherwise high D₂ occupancy, such as ziprasidone or amisulpride. However, 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 (ziprasidone), effects on sleep, decrease in cortisol levels and increase in neurotrophic growth factors [12].

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