

## Atypical antipsychotics for mood and anxiety disorders: Safe and effective adjuncts?

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In the past, typical antipsychotic medications were commonly used with antidepressant drugs for the treatment of severe depression accompanied by psychotic symptoms. When the atypical antipsychotics became available, clinicians started to use them largely on the basis of their less problematic side effect profiles. Indeed, these drugs produce fewer, if any, extrapyramidal symptoms, and they are sometimes defined on that basis. Alternatively, they may be defined as agents with a greater affinity for serotonin (5-hydroxytryptamine; 5-HT)<sub>2A</sub> binding sites than for dopamine type 2 (D<sub>2</sub>) binding sites. Their action is of an antagonistic nature at both of these receptor subtypes, and the blockade of 5-HT<sub>2A</sub> receptors is thought to lead to enhanced dopamine release in the basal ganglia, which counterbalances the antagonism of D<sub>2</sub> receptors in brain regions involved in motor control. While the clinical use of the atypical antipsychotics in the management of nonpsychotic disorders was gradually increasing, *in vivo* physiologic studies in laboratory animals were consistently indicating that these drugs exert effects on the monoaminergic systems that resemble those of certain antidepressant medications.<sup>1-3</sup> For at least some of these drugs, such findings were not surprising, given their *in vitro* neurochemical profiles.<sup>4</sup> For example, the atypical antipsychotic risperidone has an affinity for the  $\alpha_2$ -adrenoceptor that is as high as its affinity for the D<sub>2</sub> receptor; it is also in the same range as that for the antidepressant mirtazapine, which is believed to act mainly through this  $\alpha_2$ -adrenergic receptor in the treatment of depression.<sup>5</sup> Quetiapine also has an affinity for  $\alpha_2$ -adrenoceptors that is higher than for 5-HT<sub>2A</sub> receptors.<sup>4</sup> For olanzapine, however, there is little similarity between its neurochemical profile and those of the antidepressants, apart from its antagonistic activity at 5-HT<sub>2A</sub> receptors.<sup>4</sup>

In the late 1990s, clinical reports were emerging on the beneficial actions of risperidone in obsessive-compulsive disorder and treatment-resistant unipolar depression.<sup>6,7</sup> The double-blind study of Shelton et al published in 2001,<sup>8</sup> which showed a robust and rapid antidepressant effect of olanzapine addition in patients with fluoxetine-resistant depression,

catapulted research endeavours in this field. Although this study was carried out on a small number of patients, its credibility was enhanced by the inclusion of an olanzapine-only arm (in which treatment was not effective); because the side effects of olanzapine can be rather conspicuous, this design helped to maintain the blinding in the study. Since then, several trials have shown a beneficial effect of atypical antipsychotic addition to antidepressants in unipolar and bipolar depression.<sup>9-13</sup> Furthermore, there is growing evidence that these drugs may be endowed with mood-stabilizing properties. Given that a significant proportion of patients with bipolar disorder cannot be brought to and maintained in euthymia with mood stabilizers alone, the concomitant use of atypical antipsychotics has thus become widespread, and this approach is supported by several randomized controlled trials.<sup>14</sup>

An important feature of using atypical antipsychotics in mood disorders is that they can be effective at doses that would be considered subtherapeutic for the management of psychotic disorders. For instance, in a large open-label trial of patients with depression resistant to treatment with selective serotonin reuptake inhibitors (SSRIs), in which dose determination was largely left to the clinician according to side effects and response, the mean dose of risperidone was 1.1 mg/day.<sup>9</sup> Consequently, for such indications, these drugs may be perceived more as augmentation tools than as antipsychotic agents. All of these positive aspects of atypical antipsychotics have led some clinicians to use them as first-line augmentation in patients with treatment-resistant disease.

There are, however, several issues to consider before the atypical antipsychotics are used as augmentation strategies for unipolar depression. First, in patients with schizophrenia these drugs have been reported to elevate blood lipids and glycemia, sometimes independently of weight gain.<sup>15</sup> In rare cases, the elevations have been catastrophic. Therefore, some monitoring of these biological parameters should be instituted to ascertain if such a metabolic syndrome is developing. In contrast, the possibility of tardive dyskinesia with low

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doses of atypical antipsychotics is probably less likely than when these drugs are used at the higher doses typical for psychotic disorders, for which the likelihood is already very low. Second, although the atypical antipsychotics are undoubtedly effective on a short-term basis, their utility in maintaining the antidepressant response remains to be established. The only long-term double-blind data are for risperidone prolongation.<sup>16</sup> In that study, the time to relapse was not significantly different from a placebo switch after remission was achieved. In the community, physicians sometimes report fading of the antidepressant response of risperidone. Clearly, more data are needed to determine, for instance, if this result was a function of the trial design. More long-term data are also needed from studies involving more than one agent from this class of drugs. Such data should become available in the coming years because of their widespread use in bipolar disorder.

Given these considerations, it may be prudent to use either antidepressant drugs or agents with a longer track record, such as lithium, in first-line augmentation or combination therapy for treatment-resistant unipolar depression. The atypical antipsychotics may then be considered as a second-line strategy for this indication.

In patients with obsessive-compulsive disorder, however, the pharmacotherapeutic options for SSRI-resistant disease are almost nonexistent. Apart from multiple case series, the effectiveness of risperidone addition is also supported by 3 double-blind studies.<sup>6,17,18</sup> The results with olanzapine have not been so consistent,<sup>19,20</sup> although quetiapine addition appears promising on the basis of results from a double-blind study.<sup>21</sup> Although all atypical antipsychotics appear to be effective in treatment-resistant depression, this does not seem to be the case for treatment-resistant obsessive-compulsive disorder. The mechanism of action of these drugs may thus be different in these 2 disorders. Finally, there have been reports that the atypical antipsychotics are beneficial as an augmentation strategy in post-traumatic stress disorder.<sup>22</sup>

In summary, the use of atypical antipsychotics has recently emerged as an effective strategy in treatment-resistant mood and anxiety disorders. As there is now a consensus that depression must be treated rapidly and aggressively, this new therapeutic option is certainly a valuable addition to our armamentarium. More data are necessary before this option can be considered as a first-line strategy for depression, but in patients with treatment-resistant bipolar disorder and obsessive-compulsive disorder, some of the atypical antipsychotics may be considered as a first-line approach.

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