Major depressive disorder (MDD) does not always respond to antidepressants. Whether we are using SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics, monoamine oxidase inhibitors, or heterocyclics (trazodone, nefazodone, bupropion), the result often falls short of full remission of symptoms.

Consequently, we see much switching around among agents, use of 2 or even 3 antidepressants at once, co-treatment with minor tranquillizers, strategies to add lithium or thyroid supplementation, and long trials of various kinds of psychotherapy. For patients whose depression is truly resistant to pharmacotherapy, it is often necessary to resort to electroconvulsive therapy or, more recently, vagal nerve stimulation, repetitive transmagnetic stimulation, or even direct brain stimulation. Atypical antipsychotics also get thrown into the treatment mix. The good news is that the medications are sometimes very helpful; the bad news is that they carry a risk of serious adverse effects. It is not entirely clear whether the beneficial effect of atypical antipsychotics in treating depression is a class effect or a unique property of only certain agents. Pharmaceutical company interest is high, given the great prevalence of MDD in the population, much higher than schizophrenia or bipolar disorder (until recently, the only FDA indications for atypical antipsychotics). Evidence of the usefulness of atypical antipsychotics in treating MDD goes back more than 7 years. A controlled trial found that the combination of olanzapine and fluoxetine was more helpful in treating patients with MDD (without psychosis) than fluoxetine or olanzapine alone.\(^2\) The group that received combination therapy did significantly better than the others.\(^2\) However, the combination of olanzapine and fluoxetine (marketed as Symbyax) remained targeted at treating bipolar disorder, especially when symptoms of depression prevailed.

**Aripiprazole**

In November 2007, the FDA approved aripiprazole as the first atypical antipsychotic to treat MDD. It is specifically for adjunctive treatment, along with an antidepressant, for the treatment of refractory MDD. Several clinical studies support this indication. For example, Berman and colleagues\(^3\) started out with more than 1000 patients with a history of 2 to 4 failed antidepressant trials for their current episode of MDD. All qualified patients then underwent a 6-week prospective treatment phase with an SSRI or an SNRI to establish nonresponse. Including only confirmed nonresponders, they randomly and blindly assigned 182 patients to take aripiprazole and 176 patients to take placebo in addition to the antidepressant they were already taking. Approximately 1 in 4 patients who had just shown unresponsiveness achieved remission at the end of a 6-week treatment period with adjunctive aripiprazole.\(^3\) The starting dose of aripiprazole was 5
mg, and the mean dose at the end of double-blind treatment was 11.8 mg, lower than the usual dose required for treating bipolar disorder and schizophrenia. Adverse effects and drop-out rates were relatively low, with akathisia and weight gain (+2.01 kg) being the most troublesome for those in the aripiprazole group.

**Risperidone**

In 2007, just as aripiprazole was getting limited approval for treating MDD, an important study was published showing similar efficacy for risperidone. Mahmoud and associates enrolled patients with MDD from 75 primary care and psychiatric centers. After a 4-week run-in period, 268 patients were randomly assigned to either placebo or risperidone. Patients in the risperidone group received 1 mg/d for 6 weeks (in some cases increased to 2 mg/d after 4 weeks).

More risperidone recipients than placebo patients experienced remission of depression (24.5% vs 10.7%). Response was also better in the risperidone group (46.2% vs 29.5%). Early symptom improvement (during the first week of treatment) seemed to frequently predict eventual remission. Adverse effects of headache, somnolence, dry mouth, and weight gain were more common in the risperidone group but did not usually cause dropout from the study.

So far, I have not seen any studies reporting on the efficacy of paliperidone (the recently marketed risperidone metabolite) for treating refractory MDD.

**Quetiapine**

AstraZeneca is currently seeking FDA approval for quetiapine extended-release (Seroquel XR) to treat MDD. The dosages being studied are in the range of 50 to 300 mg/d, considerably lower than the 400 to 800 mg/d for schizophrenia or bipolar disorder. Pooled evidence from 8 clinical studies was recently presented to the FDA Psychopharmacologic Drugs Advisory Committee.

In 6 of 7 short-term studies, quetiapine extended-release, given at doses of 50 to 300 mg, proved effective. Superiority over placebo occurred within the first week of treatment, in marked contrast to the usual delayed response seen with traditional antidepressants. Overall, results were positive in 7 of 8 studies. This compares favorably with most placebo-controlled studies that usually show that antidepressants are better than placebo in only half of the controlled studies. (At the same meeting, there was also discussion of studies trying to establish a role for quetiapine in treating generalized anxiety disorder, where there seemed to be some agreement about efficacy but not safety.)

Members of the FDA Advisory Committee also noted adverse effects, such as tardive dyskinesia, metabolic changes, and even (possibly) sudden cardiac death, as worrisome. Some kind of limited approval is likely for quetiapine to treat MDD, perhaps for use only after first-line treatments have failed.

**Ziprasidone**

A couple of trials have suggested a positive effect for ziprasidone augmentation in treating refractory MDD. However, the results are not conclusive given the low numbers of patients involved and the open design of the trials.

**Conclusion**

There is emerging evidence supporting the usefulness of atypical antipsychotics in the treatment of MDD. The studies primarily show effect when atypical antipsychotics are used as add-on agents to traditional SSRIs and SNRIs in patients with refractory depression. So far, quetiapine extended-release and aripiprazole have the best documentation. The effectiveness of relatively low doses and a quick response are both very encouraging findings.

What is not yet clear is how long these agents need to be continued and how severe the metabolic (weight gain, hyperlipidemia, diabetes), CNS (akathisia, parkinsonism, tardive dyskinesia, neuroleptic malignant syndrome), endocrine (hyperprolactinemia), and possible cardiac conduction adverse effects will prove to be in patients with MDD.

Until we are better able to quantify the risks with carefully controlled clinical trials assessing the risks and benefits of long-term treatment, it makes sense to keep patient exposure as short as possible. That would be in marked contrast to usual practice with traditional antidepressants, where the bias is in the direction of maintenance for anyone with multiple episodes and/or severe symptoms.

**References:**


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