What is the most appropriate name to describe the newest generation of atypical antipsychotics?

The most appropriate name would be third-generation antipsychotics. The first-generation antipsychotics were the phenothiazines; the second generation was everything else (ie, butyrophenones, thioxanthenes, etc); and the most recent would be the third generation. They are a diverse group but are different enough from the neuroleptics—the first- and second-generation antipsychotics—to warrant their own category.

Are the newer atypical antipsychotics mechanistically different than the older ones?

All antipsychotics act on dopamine (D₂) receptors and have some level of serotonin (5-HT₂) blockade as well. The 5-HT₂ receptor is linked to a D₂ receptor such that when it is stimulated, it makes D₂ receptors more sensitive to blockade, and if the D₂ receptor is blocked, it mitigates some of the effects of blocking the D₂ receptors, especially in the basal ganglia. The older neuroleptics are all 5-HT₂ antagonists and D₂ antagonists. They have relatively more D₂ antagonism than 5-HT₂ antagonism. With the newer atypical antipsychotics, the amount of D₂ blockade has been turned down and the amount of 5-HT₂ blockade turned up.

The major selling point of these newer antipsychotics is that they are more effective in treating negative symptoms than the conventional neuroleptics. Has this been supported by ongoing research?

This observation has not been supported by research. With the exception of clozapine, all of the newer antipsychotics have been studied in industry-sponsored randomized trials where they are compared with a placebo and an active comparator—haloperidol. Haloperidol is very potent in D₂ blockade. Blocking this receptor results in many deficits in the ability to generate and coordinate behavior, whether motor behavior, emotional behavior, or thought. Thus, patients taking haloperidol have more bradykinesia and blunted affect. When compared with relatively less D₂ blockade, there seem to be fewer negative symptoms from an antipsychotic.

Further, very drug-naïve patients enter these randomized trials. Most of these patients have been on a neuroleptic. When switched to one of the third-generation atypical antipsychotics, they get less D₂ blockade and less blunting; they seem to brighten up a little bit and their negative symptoms seem to improve. This is because the drug itself is not producing as many negative symptoms.

There are two major flaws in these comparisons. First, they are using higher doses of haloperidol and, therefore, getting more side effects. Thus, the drug being studied is always going to look
better than a higher dose of haloperidol. Second, they are not addressing the haloperidol level by blood vessel to see whether it is even the right dose to treat the disorder.

Are the newer antipsychotics more effective in symptom control for schizophrenia?

Of the newer drugs in schizophrenia, the one drug that seems to be more effective than any other for negative cognitive symptoms is clozapine. The newer drugs have less D2 blockade and produce less cognitive Parkinsonism. In comparison to haloperidol, there is less blunting of thought and cognitive functioning is better.

The core cognitive deficit of schizophrenia is a defect in sensory gating (ie, the inability to shut off irrelevant information and to tell the difference between relevant and irrelevant sensory input). Clozapine is the only antipsychotic that is to some extent effective in correcting that deficit. The other thing that corrects the gating deficit is smoking. The defect in sensory gating is due to a malfunctioning gene for a type of acetylcholine receptor called the α7 nicotinic receptor, which nicotine acts on. Thus, acute-inhaled nicotine will correct the gating deficit in schizophrenia. Some research suggests that clozapine works better in heavy smokers and that people who respond to clozapine are more likely to stop smoking. This is because clozapine, unlike other antipsychotics, corrects that gating deficit.

Research suggests that olanzapine and quetiapine may somewhat help the gating deficit, but they do not benefit as much as clozapine.

Are the newer antipsychotics more effective in symptom control for mood disorders?

All antipsychotics are effective for mania. In equivalent sedative doses, the newer ones are not more effective for mania than the older ones. Benzodiazepines, and before that barbiturates, used to be the mainstay of the treatment of mania years ago. Anything with sedatives, and especially antipsychotic properties, will work acutely for mania.

It is more difficult to determine the effectiveness of maintenance treatment for mood disorders. One must observe how the drug companies have designed their studies. Unlike with schizophrenia, there is no analog of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) study for bipolar disorder. The studies are entirely industry-sponsored studies.

In the pivotal trial for olanzapine monotherapy, slightly <550 patients with bipolar I were treated openly with olanzapine plus lithium. Of that group, ~120 patients over 6 weeks could not stay in the study and were kicked out. The remaining ~430 were felt to be remitted, meaning they had a Young Mania Rating Scale score ≤12 and a Hamilton Rating Scale for Depression score ≤8. Thus, remitted meant 33% to 50% were as symptomatic as they were when they started. Those patients were randomized to ~20 mg olanzapine in decent doses or lithium in a therapeutic dose for 1 year. Investigators found that more olanzapine than lithium patients completed the study (~47% of the olanzapine patients and ~33% of the lithium patients), and there were fewer relapses to mania in the olanzapine study. However, rates of relapse into any affective episode or relapse into a depressive episode were about the same with both drugs.

As with all industry-sponsored studies of bipolar disorder, the sample was enriched: patients who were anticipated to respond in the first place were treated openly, anyone who did not respond openly was kicked out, and the ones who did seem to respond were placed into the randomized trial. At the end of the study, these patients were not well on monotherapy with any of the drugs. They were less symptomatic and had fewer acute episodes, but they were still ill. None of these kinds of studies conduct any measures of functioning or quality of life.

It is also important to note that such studies always exclude patients who are suicidal, are active substance abusers, or have any meaningful comorbidity. However, 80% of people with bipolar disorder are substance abusers. Thus, one cannot extrapolate to real life from these studies.

The same study method is used for the drugs that have now some labeling for maintenance of mood disorders (olanzapine and quetiapine). Quetiapine just had an add-on maintenance study published last year. It is the same method with all the studies conducted. The study conductors take patients who respond well acutely, randomize them, and get about the same results with lithium or sometimes divalproex sodium. In an add-on study, they add one of these drugs or a placebo onto lithium or divalproex sodium, and they get less relapse. However, is this the antipsychotic effect of the drug? These are sedating drugs. Is it the fact that patients sleep better and once they sleep better, their moods are better—or is it that the rating scale scores emphasize insomnia, talking a lot, and agitation, and all of those are going to be better with a sedating drug?

I would like to see a study using diazepam, lorazepam, or clonazepam as a control—the latter two were at one time a mainstay of the treatment of bipolar disorder—and see whether or not there are better results with the antipsychotics.

Is the long-term risk of tardive dyskinesia lower with the new-generation antipsychotics?

First-generation antipsychotics were introduced in the 1950s and tardive dyskinesia was not identified until the late 1970s. Tardive dyskinesia has been reported with all of the atypical antipsychotics, including the newer ones. Though there have been fewer reports with the newer antipsychotics so far, it is yet unclear what long-term experience will show.

Are there any good data on compliance rates other than the CATIE study?

The only other data are in the industry-sponsored studies. There is a relatively low dropout rate with patients on these new-generation antipsychotics compared to historic experience with the neuroleptics or sometimes compared to the comparison neuroleptic. It is hard to
I use molindone hydrochloride tablets in a low dose for patients who should not or do not want to gain weight. It is certainly as good as risperidone and some of the other atypical antipsychotics that have more D₂ blockade. There is not a tremendous amount of difference between the amount of D₂ blockade or extrapyramidal side effects between risperidone and a drug like molindone hydrochloride, but the latter is much less likely to cause weight gain than risperidone is. I use molindone hydrochloride and loxapine for psychotic depression. I have used all of the newer-generation antipsychotics for psychotic depression as well, almost always in combination with an antidepressant.

I use aripiprazole for some very refractory depression, with or without psychosis, and I find it to be unpredictable. Sometimes I have had very good results with it, but it is very hard to find the right dose. There is a lot of akathisia with it and a lot of blunting if the dose is raised too high. It is very hard to find the right dose with depressed patients, but it is less likely to cause weight gain than some of the others. I use ziprasidone for some severely depressed patients, but it is also unpredictable. Even though it causes less weight gain, it makes a lot of people very jittery and it cannot be combined with other serotonergic drugs easily because it is a selective serotonin reuptake inhibitor.

**REFERENCES**


**What drives your choice to prescribe one antipsychotic over another?**

Though it is never a first choice, I use clozapine for very refractory schizophrenia. It is difficult to take, but it works better than the other antipsychotics. Most schizophrenic patients who are given clozapine are in a clozapine group, and so there is more effort put into other forms of therapy in addition to the medication that may explain some of the benefit. However, I have seen people who did very poorly on everything except for clozapine.

There were studies a number of years ago showing that the combination of a neuroleptic and an antidepressant worked very well for negative symptoms of schizophrenia in schizophrenic patients who were not depressed but who had a family history of depression. This suggested that depression in the family is somehow a marker of response to antidepressants in a patient with negative symptoms but with no real depressive symptoms. Thus, at times I combine an antidepressant with a drug like clozapine.

I also use clozapine for very intractable and severe ultradian cycling in bipolar patients. However, bipolar patients do not tolerate clozapine nearly as well as schizophrenic patients. They have much less patience themselves for the problems taking this medication, and so they are less likely to agree to it. Still, it works well when they need it.

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