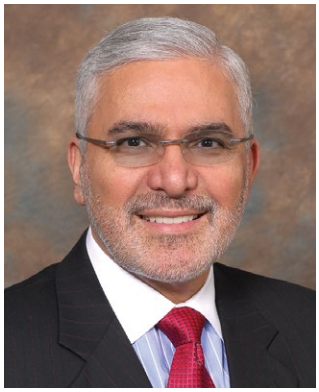

Henry A. Nasrallah, MD
Editor-in-Chief

Pimavanserin: A potentially safer alternative to clozapine for refractory hallucinations and delusions

Up to 30% of patients with schizophrenia do not respond to dopamine antagonists, which include all first- and second-generation antipsychotics. They are labeled as "treatment-resistant" if they have a partial response, or "treatment-refractory" if their hallucinations and/or delusions do not improve at all despite multiple trials of antipsychotics.

Our clinical team made a serendipitous discovery about the efficacy of pimavanserin in patients with schizophrenia who failed to respond to clozapine therapy

That's why clozapine is considered a "lifesaver" for such patients, a last-resort medication that unshackles patients with refractory psychotic symptoms from the tyranny of auditory and/or visual hallucinations and the reality distortion of fixed false beliefs such as paranoid delusions.

Many long-suffering patients with refractory psychosis recover and return to their baseline, thanks to clozapine. In a past editorial, I discussed how one of my patients, Bethany, who had dropped out of college and became homeless for 4 years with refractory delusions and hallucinations, recovered completely when she received clozapine.[1] She then returned to college, graduated with honors, and authored a book about her journey of recovery.[2] She and I later established a nonprofit foundation we called CURESZ (Comprehensive Understanding via Research and Education in Schizophrenia), and assembled a panel of 80 clozapine experts across the country to provide access to clozapine for the hundreds of thousands of individuals with refractory psychosis who never received a trial of clozapine from their psychiatrists or psychiatric nurse practitioners. (Visit CURESZ.org for details.)

Bethany was very lucky to respond and recover completely, because only 40% of patients with refractory psychosis respond to clozapine. She does not mind having her blood drawn every week to measure her white blood cell count for early detection of potentially fatal agranulocytosis. Many refractory, often homeless patients with chronic schizophrenia refuse to have weekly phlebotomy and therefore are not treated with clozapine. Bethany was also fortunate to experience only 1 adverse effect of clozapine: extreme sedation that forced her to sleep up to 15 hours a day (this was reduced to 9 to 10 hours a day with adjunctive modafinil). Fortunately, she was spared the multiple other serious adverse effects of clozapine, which include excessive salivation, extreme weight

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From the Editor

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gain, diabetes, hyperlipidemia, cardiomyopathy, pancreatitis, seizures, and ileus.[3] Clozapine is also associated with sudden death more than any other antipsychotic agent.[4]

So, what can be done for patients with refractory hallucinations and delusions who are among the 60% who fail to respond to clozapine, or who experience intolerable adverse effects or safety problems, or who refuse to take clozapine and have their blood drawn every week? This is a desperately ill and seriously disabled group of patients who are deemed to be beyond the reach of medical intervention by psychiatry. They are often treated with various off-label medications as adjunctive therapy to clozapine, to which they failed to respond. This includes adding lamotrigine[5] or benzoate,[6] but none have been approved as an efficacious and safe monotherapy alternative to clozapine. So, what can be done for patients with refractory illness?

Enter pimavanserin. This new medication is an inverse agonist of serotonin 5-HT2A receptors and (to a lesser extent) serotonin 5-HT2C receptors. It was recently FDA-approved for treating the hallucinations and delusions of Parkinson's disease psychosis,[7] which is estimated to develop in up to 50% of individuals with Parkinson's disease. It does not have any affinity to any dopamine receptors, which makes it an ideal antipsychotic for Parkinson's disease, where any dopamine antagonism can worsen the motor symptoms (rigidity, hypokinesia, and tremors) associated with that movement disorder. Thus, pimavanserin became the first ever non-dopaminergic antipsychotic in the world and is indicated only for Parkinson's disease psychosis.

Our clinical team made a serendipitous discovery about the efficacy of pimavanserin in patients with schizophrenia who failed to respond to clozapine therapy after several months at clinically adequate doses. Our findings were published online last month in the highly respected journal *Schizophrenia Research*.[8] We reported the successful treatment with pimavanserin in 2 groups:

- patients who had not responded to clozapine received pimavanserin as an *add-on* to clozapine in doses of 34 mg/d, the same dose recommended for patients with Parkinson's disease hallucinations and/or delusions.
- patients who had hallucinations and delusions that failed to respond to several non-clozapine antipsychotics received pimavanserin monotherapy *instead of* clozapine to avoid blood draws and serious adverse effects.

Pimavanserin successfully treated the hallucinations and delusions of all 10 patients in both groups. Remission occurred within 1 month in most cases, and after 2 months in 1 patient. Those patients no longer required hospitalization as they did prior to taking pimavanserin, and they maintained their response for several months of follow-up. We were also pleased to note that most patients became more sociable and affable, with improved mood and affect, after their hallucinations and delusions disappeared with pimavanserin. We did have a few patients who did not respond to 34 mg/d of pimavanserin, and some who responded for several months but then showed signs of recurrence. We are considering increasing the dose to 68 mg/d in such patients because it is possible that a higher dose may be needed in some patients with refractory illness, who may vary in symptom severity or biology.

We are now planning to apply for a research grant to conduct a controlled trial to confirm our very encouraging clinical findings, and we hope other investigators will also conduct clinical trials in patients with refractory psychosis comparing pimavanserin with

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placebo or pimavanserin with clozapine in double-blind studies.

As a disclosure, our clinical findings were obtained without any knowledge of, or funding from, the company that makes pimavanserin (Acadia Pharmaceuticals Inc.). The company was informed of our findings only after our article was accepted for publication.

I hope this important finding of a potentially safer alternative to clozapine may address a major unmet need in psychiatry, involving the treatment of hundreds of thousands of patients with treatment-resistant or treatment-refractory psychosis, which includes patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder.

Pimavanserin successfully treated the hallucinations and delusions of all 10 patients in both groups

Henry A. Nasrallah, MD
Editor-in-Chief

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