

Clozapine is a vastly underutilized, unique agent with multiple applications

Psychiatrists know that clozapine helps many patients who have intractable psychotic symptoms that have failed to respond to trials of several antipsychotics.

Since clozapine was launched in 1989, miraculous improvements and “awakenings” have been reported in many patients afflicted with severe schizophrenia and considered hopelessly refractory to antipsychotic pharmacotherapy. Not only do severely disabled patients regain their sanity and return to normal functioning, but the joy that their family and treating psychiatrist experience is priceless.

That’s why I am perplexed by how infrequently clozapine is used in the United States (in about 5% of patients)—even though approximately 25% of patients who have schizophrenia are either treatment-resistant or have refractory hallucinations or delusions.

Consider Bethany’s case. She was one of my young patients, who, after taking clozapine, recovered fully and resumed a productive life, after years of homelessness during which she was controlled by auditory hallucinations.

Bethany’s story began well...

Bethany grew up in a loving home, smart and talented, an “A” student in high school and talented violin-

ist. She received a scholarship to a prestigious private university at 16 and left her parent’s home in Ohio to major in molecular biology. Her goal was to attend medical school. She excelled during her first 3 years of college, and even published 2 papers in top-tier science journals.

In her senior year, after returning from a trip to Africa, Bethany began to change. She neglected her studies and focused on raising money for HIV clinics in Africa. She began getting F’s instead of A’s, lost her scholarship and her residence hall room, and had to drop out of college. Soon, she began hearing voices commanding her every action.

...but took a really bad turn

Bethany became homeless for the next 4.5 years. She ate discarded food from garbage cans, had no change of clothes, and slept on a concrete slab behind a downtown church in a major city in California. Her parents lost track of her, although her mother, a retired nurse, frantically and relentlessly tried to find out what happened to her only daughter during that time.

Eventually, Bethany was arrested when she was found screaming back at the voices, at midnight in a residential area of the city. She was hospitalized on a psychiatric ward and given antipsychotics, but with only modest improvement.

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Clozapine has the potential to have a healing effect for many patients whose schizophrenia is resistant to treatment

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Figure

Schizophrenia: 2 stories of 1 family



Both books that describe the Yeiser family's struggles can be purchased at www.amazon.com

marshal in the commencement ceremony procession.

Over the next year, with strong encouragement, Bethany wrote a book about her remarkable recovery from refractory psychosis.¹ In addition, her mother wrote a deeply emotional book that described the gut-wrenching ordeal that she and her husband went through during the years that Bethany disappeared.² I urge you to read these inspiring books (*Figure*) about the remarkable recovery from refractory psychosis and the heavy family burden of schizophrenia.

Her parents were contacted; immediately, they flew to California to see her. The treating psychiatrist told them that their daughter had schizophrenia, and that they should lower their expectations because she would be totally disabled for the rest of her life. They brought Bethany back to Ohio where, after a tumultuous year of failed trials of several antipsychotics to suppress the auditory hallucinations, we gave her clozapine.

Gradually, Bethany improved, but she still could not read a book or magazine (which I urged her to do) without the voices intensifying and preventing her from reading.

Bethany recovers

After 6 to 8 months on clozapine, however, Bethany's auditory hallucinations faded away. With my encouragement, she enrolled at the University of Cincinnati and took 1 course at a time. She began to get A's again—in advanced courses, such as genetics, physics, and molecular biology. She completed her degree requirements and graduated with honors, with a Bachelor of Science degree in molecular biology. She also served as a

Back to clozapine

Although the package insert for clozapine contains 5 black-box warnings (for agranulocytosis, seizures, myocarditis, respiratory effects, and increased mortality in geriatric patients with psychosis associated with dementia), the drug is a useful last-resort medication for several approved indications and off-label uses. In addition to the official, evidence-based indication for treatment-resistant and refractory schizophrenia,³ clozapine is FDA-approved for suicidality in schizophrenia.⁴ Clinically reported, but unapproved, uses are listed in the *Table*.⁵⁻¹³

A little-known advantage of clozapine is its salutary effect on mortality. In a Finnish study of 66,881 persons who had schizophrenia,¹⁴ those taking clozapine had, overall, lower mortality during the treatment period than those taking any of the 6 most commonly used antipsychotic drugs.

No doubt, clozapine is associated with serious side effects¹⁵—but so is chemotherapy for cancer, and oncologists do not hesitate to use it to save their patients from physical death. Severe schizophrenia is like a can-

cer of the mind, and *clozapine is its chemotherapy*.

Fortunately for Bethany, she had almost no physical adverse effects from clozapine except for intense sedation, which was mitigated with modafinil.

We should use clozapine more than we do

Clozapine has the potential to have a healing effect for many patients whose schizophrenia is resistant to treatment. Most such patients, however, never receive a trial of the drug. Furthermore, few practitioners use clozapine for schizophrenia patients with suicidal tendencies, despite the high rate of suicide completion in schizophrenia.¹⁶

Clozapine remains, regrettably, an underutilized agent in psychiatry. Until other breakthrough drugs are discovered, its use ought to be double or triple what it is now because there are many people like Bethany who are not being given a chance to recover from their illness.



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Table

Clozapine has several off-label uses

Aggression and violent behavior during psychosis ⁵
Delusional disorder ^{6,7}
Idiopathic psychosis in Parkinson's disease ⁸
Polydipsia and water intoxication ⁹
Severe borderline personality disorder ^{10,11}
Tardive dyskinesia ⁹
Treatment-refractory bipolar mania ¹²
Treatment-resistant depression ¹³

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Severe schizophrenia is like a cancer of the mind, and clozapine is its chemotherapy