Episode 049: Clozapine for Treatment Resistant Schizophrenia

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There are no conflicts of interest for this episode.

On today's episode of the podcast, Dr. Cummings and I talk about clozapine, a medication that treats schizophrenia.

What is clozapine?

Not only is clozapine the gold standard medication for treatment-resistant schizophrenia, it is also one of the most unique drugs used in psychiatry.

It was synthesized 1958, only eight years after chlorpromazine, the first antipsychotic drug, was created. At that time, researchers tested for antipsychotic properties by taking various compounds and testing to see if lab mice developed dystonia and catalepsy. When researchers tested clozapine, they found that it did not cause dystonia, but instead made the mice sleepy. Because of this, clozapine was almost missed entirely as an antipsychotic medication. Eventually, however, clozapine was found to be more successful than other antipsychotic drugs.

By the 1970s, Austria, Germany, and Finland had produced positive data on clozapine proving its efficacy. However, clozapine was also found to have caused severe neutropenia in sixteen patients in Finland, and even caused the death of eight of those patients. For this reason, clozapine did not enter the United States until it was approved by the FDA in 1989.

Defining "Treatment-Resistant" Schizophrenia

Clozapine was approved largely due to the work of John Kane. In his work, Kane helped define "treatment-resistant" schizophrenia, and ultimately the context in which clozapine has proven benefits. The term "treatment-resistant" can be defined as schizophrenia

that has failed to respond to an adequate dosage of two antipsychotic medications given for an adequate duration:

- The dosage should be a minimum of 600-1000 mg chlorpromazine equivalents.
- Duration should be a minimum of six weeks.
- Additionally, patients must have failed a prospective trial of haloperidol 15 mg given daily.

With this definition, Kane and his team found that a patient's odds of responding to clozapine was 50-60%, whereas the probability of responding to other antipsychotic medications was 0-5% (with an average response of 2%). Today, these rates are essentially unchanged.

In 2017 Howes et al. found similar response rates to clozapine. The team largely followed Kane's original criteria for treatment-resistant schizophrenia but did not include the failed prospective trial of haloperidol. Additionally, the team measured plasma levels of clozapine to assess patients' adherence. Ultimately, they found that the odds of responding to clozapine was 40-60% while the odds of responding to other antipsychotics was 7% or less.

In contrast, there have been meta-analyses, including Cochrane, suggesting that clozapine is not more effective than other antipsychotics. However, these studies have failed to strictly define or include "treatment-resistant" schizophrenia criteria. It is likely that schizophrenic patients who were not truly treatment-resistant were included in those studies. In this context, clozapine is not more effective than other antipsychotic medications.

Unique Effects

In addition to being the gold standard for treatment-resistant schizophrenia, clozapine has other unique effects. It has been found to reduce both suicide and violence in patients, independent of the drug's antipsychotic effects. Criminal behavior is also decreased. Clozapine can also be used to treat psychogenic polydipsia and refractory mixed bipolar states.

Mechanism of Action

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Part of the reason that makes clozapine so unique is its mechanism of action. Typically, second generation antipsychotics antagonize dopamine but more selectively than their first generation counterparts. Additionally, atypical antipsychotics antagonize the 5-HT2a receptors, which actually assist with dopamine transduction in the frontal lobe. Although clozapine does have atypical antipsychotic properties, it also works by modulating glutamate signal transduction, particularly in the frontal and temporal lobes. Even at high plasma levels, the concentration of clozapine at the D2 and D3 receptor is only 30-40%. It is the modulation of glutamate that helps stimulate and “awaken” the hypoactive brain of a schizophrenic patient.

Improving glutamate decreases the positive symptoms, improves the negative symptoms, and even helps with cognitive symptoms. Clozapine’s unique mechanism of action may be why Krakowski et al (2006) found that although clozapine, olanzapine, and haloperidol had approximately the same reduction in psychosis for violent schizophrenic patients, clozapine was superior to olanzapine and haloperidol in decreasing violence in the same patients because it significantly mediated the executive function of the frontal lobe.

Other than glutamate, clozapine does affect other key molecules and receptors. The major daily side effects are most likely due to the blockade of the His-1 receptors, and the subsequent sedation may become a dose-limiting side effect for the patient, especially at higher plasma levels of clozapine. Alpha-adrenergic antagonism also contributes to the drug’s side effect profile, such as hypotension. Additionally, although clozapine’s robust and positive effect on glutamate likely overrides much of the drug’s anticholinergic effects, there is still the chance for anticholinergic burden, especially if the patient is taking other anticholinergic medications.

Target Dose and Medication Adherence

It is vital to maintain a therapeutic alliance with a patient on clozapine, as noncompliance is a major factor for treatment failure in schizophrenic patients. For example, the adherence rate for antipsychotic medications in general is less than 40%. This is partially alleviated with long-term injectable agents, but clozapine does not have

this option. The only forms of clozapine are tablets, wafers, and liquid agents. Therefore, it is beneficial to schedule regular meetings with patients on clozapine.

One method to assess medication adherence is by checking plasma concentrations and blood levels of clozapine. If patients are adherent, their plasma concentration of clozapine should be fairly consistent. Obtaining blood levels also assures the provider that the current medication dose is optimal, as patients vary in metabolism and absorption rates and other factors, such as smoking and different medications, can also affect hepatic metabolism.

To treat psychosis, the target range of clozapine should be 350-600 ng/mL. If symptoms are not adequately controlled at this level, but patients are tolerating the medication, clozapine can be gradually titrated to approximately 600-1000 ng/mL. After 1000 ng/mL there is a diminishing return of benefits and an increased likelihood of side effects. Rarely, patients will need to go above the 1000 ng/mL level. If the goal is to not treat psychosis but another issue like criminality, then patients will generally respond at much lower doses. For example, in 2014 Brown et al. found that there was a dramatic reduction in violence in seven psychopathic patients with an average clozapine concentration of 171 ng/mL.

Benefits of Clozapine

On-going, uncontrolled psychosis only leads to mental decline. Early in the disease process, patients lose 2% of their brain mass every year for the first five years, and although this decline slows after that point, it never reaches zero. Additionally, although a healthy lifestyle with adequate nutrition and exercise prevents cognitive decline, it is particularly difficult to motivate schizophrenic patients because of the nature of the disease. On average, schizophrenic patients live 20 years less than the general population.

Clozapine helps address both issues. It has been shown to slow the progress of schizophrenia than any other antipsychotic, and it has been shown to prolong a patient's lifespan. In 2017 Yoshimura et al. found that the efficacy of clozapine begins to decline about 2.8 years after a patient has been shown to be treatment-resistant. This finding along with clozapine's other benefits create the argument that clozapine should

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be prescribed sooner rather than later to help patients suffering from treatment-resistant schizophrenia.

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