Role of Clozapine in Treatment-Resistant Schizophrenia

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Abstract
Clozapine is effective for treating positive symptoms in approximately two-thirds of the 30% of patients with schizophrenia whose psychosis is minimally responsive to typical or atypical antipsychotic drugs at ordinary doses. The dose range at which clozapine is effective in treatment-resistant patients is 2–3 times higher than that needed in non-treatment-resistant patients. The onset of efficacy in these patients may not be until 3–6 months after initiating treatment. There are no established means of augmenting the efficacy of clozapine in treatment-resistant patients, but electroconvulsive therapy has empirically been found to be effective in those whose psychotic symptoms persist despite an adequate trial of clozapine monotherapy. Optimal treatment with clozapine requires attention to psychosocial needs and rehabilitation of patients whose work and social function is usually impaired due to cognitive dysfunction and persistent psychosis. No other antipsychotic drug has been robustly shown to be as effective as clozapine for this group of patients. In addition, clozapine is indicated for patients with schizophrenia who are intolerant to other antipsychotic drugs or, due to its unique antisuicidal effect, those who are at high risk for suicide. Clozapine can also improve some domains of social and cognitive function, leading to marked improvement in overall function and quality of life. Although clozapine causes agranulocytosis significantly more frequently than other antipsychotic drugs, with required hematological monitoring of the white count, its occurrence has been reduced to <0.5% and associated mortality is now extremely rare. While clozapine also causes weight gain and other metabolic side effects, myocarditis, tachycardia, hypersalivation, and seizures, its advantages in treating positive symptoms, suicide risk, and cognitive and social function, lead to a positive benefit-to-risk ratio that make it an invaluable addition to the armamentarium for treating treatment-resistant schizophrenia.

Schizophrenia is a genetically determined brain disorder affecting about 1% of the population worldwide and usually begins in late adolescence or early adulthood [1]. It is characterized by positive symptoms (primarily delusions and hallucinations), negative symptoms (withdrawal, flat affect, anhedonia, and anergia), cognitive impairment (lower IQ, deficits in attention, executive function, working memory, long-term memory, speeded motor pursuit, and verbal fluency), mood disturbances,
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and suicidality. It is among the most costly of illnesses to treat despite its affecting only 1% of the population [2–5], and has a major negative impact on the lives of the families of patients with schizophrenia [6, 7]. In addition, it has one of the highest rates of suicide attempts and completed suicides of any psychiatric disorder [8].

**Discovery of Typical Antipsychotic Drugs**

Pharmacotherapy is the most effective means of treating the positive symptoms of schizophrenia. There were no effective somatic treatments for schizophrenia prior to the discovery of antipsychotic drugs, with the exception of electroconvulsive therapy. Chlorpromazine, the first antipsychotic drug, was serendipitously discovered during the early 1950s in the quest for an antihistamine which could diminish emergent post-anesthetic bizarre behaviors. It sparked the development of similar drugs which rapidly became the established treatment around the world. These antipsychotic drugs were found to be effective in up to 70% of patients with schizophrenia, within days to weeks, despite the fact that many of these patients had been psychotic for decades [9]. In 1957, haloperidol, a butyrophenone, was discovered and this became the most widely utilized of these agents, in part, because it was less sedative than chlorpromazine. It, like all the typical antipsychotic drugs discovered and developed between 1952 and 1989 act primarily through blockade of dopamine D2 receptors [10]. Their D2 receptor affinity is highly correlated with their average clinical dose [11].

**Discovery of Clozapine**

In the early 1960s, and continuing for decades thereafter, most clinicians believed that extrapyramidal symptoms (EPS) were an indicator of effective antipsychotic drug action. Failure to produce EPS was considered a sign of a weak antipsychotic drug, inadequate dosage, or both. However, EPS such as parkinsonism, dystonias, neuroleptic malignant syndrome, and eventually tardive dyskinesia developed in a high proportion of patients and led to non-compliance. Thus, antipsychotic drugs which did not cause EPS, but which blocked apomorphine- or amphetamine-induced locomotor activity (markers of antipsychotic activity), were sought using the absence of/or reduced catalepsy as a marker. In this effort, clozapine (a dibenzodiazepine) was synthesized in 1958 at the Wander Laboratories in Berne, Switzerland, by G. Hunziker, J. Schumutz, and E. Stille [12, 13]. It proved to be the first antipsychotic drug which dissociated antipsychotic activity and motor side effects. The Wander Co. was then acquired by Sandoz Pharmaceuticals, based in nearby Basel, Switzerland. The first limited open clinical experience with clozapine was not positive, possibly because clinicians did not know how to properly titrate or dose it, and did not allow sufficient duration of treatment for its full benefits to emerge.
In 1969, clozapine was finally made available for better planned clinical trials in Australia and Europe. The first positive trial, a multicenter study in Switzerland and Germany, demonstrated efficacy comparable but not superior to that of chlorpromazine [14]. Subsequent uncontrolled [15–20] and controlled studies [21–28] demonstrated clozapine to be an effective treatment for schizophrenia, with a remarkably lower risk of EPS. Importantly, the lower risk of clozapine to cause tardive dyskinesia was discerned, and its ability to diminish and even eliminate the symptoms of tardive dyskinesia was reported [29, 30]. The lack of EPS in animal models and patients led to clozapine being labeled an ‘atypical’ antipsychotic drug by the preclinical and clinical investigators who were intrigued by its differences from the early group of antipsychotics [13]. Side effects such as increased risk of seizures, hypersalivation, tachycardia, hypotension, and weight gain were noted in the early clinical trials [15, 16]. Taken together, these were not considered sufficient to discourage further clinical usage and research.

First Report of Agranulocytosis

The report that agranulocytosis occurred in 17 (0.7%) of 2,260 Finnish patients treated with clozapine, 8 (47%) of whom subsequently died from secondary infection, led to its immediate withdrawal from clinical use worldwide [31, 32], even though an epidemiological study failed to establish clozapine as the causal agent [33]. It is of interest, that no such cluster of cases of agranulocytosis has ever occurred again in Finland or elsewhere, suggesting that there may have been some secondary factor which caused this singular event [34]. The withdrawal produced rapid and severe relapse in many cases, a special problem with clozapine which rarely occurs as rapidly and severely with other antipsychotic drugs [35]. It is now established that clozapine should never be stopped abruptly, unless there is a medical necessity such as agranulocytosis or cardiovascular complications [35]. Because of the plight of those withdrawn from clozapine, it was reintroduced for humanitarian purposes in some countries within a relatively short period of time, but restricted to use in hospital settings, with monitoring of the white count. After its reintroduction following the Finnish episode, its use was not confined to special indications such as treatment-resistant or neuroleptic-intolerant patients. I am aware of no publications recommending any special indication in treatment-resistant patients from that era.

US Clozaril Study: Demonstration of Efficacy in Treatment-Resistant Schizophrenia

Clozapine was also withdrawn from clinical study in the USA in 1975, as it was around the world. However, it was available for some research and humanitarian purposes. During the treatment of patients with schizophrenia with extremely severe tardive dyskinesia, the idea emerged that it could also be effective in treating psychosis in treatment-
resistant schizophrenia patients [30]. This contributed to the interest of Sandoz and the FDA in the USA in testing whether clozapine might have an acceptable risk-benefit ratio in treatment-resistant patients, which would warrant a restricted label.

There are many definitions of treatment-resistant schizophrenia, from the very broad to the narrow [36]. The broad concepts focus on all types of symptoms, including negative symptoms and poor work and social function. The concept of treatment resistance embodied in the US Clozaril study was narrow: persistence and severity of positive symptoms along with functional impairment. Enrollment required three prior failed attempts to treat with antipsychotic drugs, using then standard dosages which were much higher than those understood today to be optimal for efficacy and tolerability, and a duration of at least 4–6 weeks for each trial; at the end of those trials, patients with residual positive symptoms (of moderate to severe intensity) and poor social function were considered to be treatment resistant [37]. Trials aborted because of non-compliance or intolerability were not considered as failed trials for this purpose. An example would be a chronically ill patient with persistent paranoid delusions or hearing voices on a nearly daily basis, associated with impaired social and work function, and a poor quality of life. Patients with only severe negative symptoms or cognitive symptoms, with mild positive symptoms, were not eligible. This concept of treatment resistance has since been adopted by the International Psychopharmacology Algorithm Project (IPAP; www.ipap.org) (see chapter by Elkis on the history and current definition). It has also been accepted by the Texas Medication Algorithm Project, a subsidiary of the Texas Department of Mental Health and Mental Retardation in collaboration with Texas universities [38].

A total of 268 patients who met these criteria for treatment-resistance were entered in the double-blind comparison which lasted 6 weeks. The patients were randomly assigned to either clozapine (up to 900 mg/day) or chlorpromazine (up to 1,800 mg/day). Responder criteria were: (1) ≥20% decrease in BPRS total score; (2) a Clinical Global Impression Scale (CGI) score of ≤3; (3) BPRS total score of ≤35, using 0–6 ratings. At the follow-up period, 30% of the clozapine-treated patients were categorized as responders compared to only 4% of chlorpromazine-treated patients (p < 0.01). The BPRS total score, Positive Symptom Scale score, and CGI scale were significantly improved by clozapine, even at 1 week, with significantly greater improvement throughout the follow-up period compared to the chlorpromazine-treated patients (p < 0.001). Clozapine was shown to be more effective in attenuating both positive and negative symptom scores of the BPRS compared to chlorpromazine (p < 0.001). The negative symptom score of BPRS was significantly improved by clozapine at 2 weeks (p = 0.002), while chlorpromazine showed no change in the negative symptom score throughout the follow-up period [37].

Side effects with both clozapine and chlorpromazine included sedation, hypotension, and weight gain. Side effects unique to clozapine were hypersalivation and tachycardia.

This landmark study led to the approval of clozapine in many countries for patients with schizophrenia or other psychotic disorders who failed to respond to at least two
other antipsychotic drugs or who developed intolerable EPS at doses of other antipsychotic drugs which were necessary to control psychosis. Japan approved the use of clozapine for this same purpose in 2009. As will be discussed, these approvals all included a required white blood cell monitoring program, weekly to begin with, but which has now been reduced in frequency in most countries.

No formal extension study was undertaken as part of the US Clozaril study. My colleagues and I continued clozapine not only in the responders to clozapine at 6 weeks, but also the non-responders from that trial. Subsequently, other patients who met the same criteria were treated with clozapine for longer than 6 weeks [39]. After treatment for a mean duration of 10.3 ± 8.1 months (median 7.6 months), 31/51 patients (60.8%) showed at least a 20% decrease in total BPRS at last follow-up. Patients reached the responder criterion at different time points, with only 45.2% of responders doing so by 6 weeks of treatment. These results suggested a 6- to 12-month trial may be desirable before deciding to discontinue clozapine due to of insufficient response [40, 41]. Similar results were obtained by Lieberman et al. [42] who concurred that the optimal time for a clozapine trial was 12–24 weeks.

A multicenter double-blind randomized study compared the efficacy and safety of aripiprazole and perphenazine in treatment-resistant patients with schizophrenia [43]. Treatment-resistant patients with schizophrenia had 4–6 weeks’ open-label treatment with olanzapine or risperidone to confirm their treatment resistance. Only patients who completed this open-label period and failed to respond to criteria similar to those in the US Clozaril trial entered the 6-week double-blind treatment phase. In all, 300 patients with confirmed treatment resistance were randomly assigned to aripiprazole (15–30 mg/day) or perphenazine (8–64 mg/day). The primary outcome measure was change in Positive and Negative Syndrome Scale (PANSS) score from baseline. Both aripiprazole and perphenazine treatment were associated with clinically relevant improvements in PANSS total scores from baseline. After 6 weeks, 27% of aripiprazole-treated patients and 25% of perphenazine-treated patients were responders. Improvements in quality of life considered to be clinically relevant occurred in 36% of the aripiprazole-treated patients and in 21% of those treated with perphenazine (p = 0.052). It was concluded that aripiprazole and perphenazine, at the doses used in that study, can improve the symptoms of schizophrenia in treatment-resistant patients who have failed to respond to olanzapine or risperidone. These results are inconsistent with much additional evidence that drugs such as perphenazine are ineffective in treatment resistant patients. Inclusion of clozapine in the study as an active comparator would have enhanced the credibility of the results.

Additional Evidence for Clozapine Efficacy in Treatment-Resistant Schizophrenia

There is a considerable amount of other literature which support the results of the US Clozaril study indicating the superiority of clozapine for treatment-resistant patients.