

Clozapine: The Commitment to Patient Safety

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Clozapine represents the “gold standard” therapy for treatment-resistant schizophrenia including use for symptom reduction and use in patients intolerant of extrapyramidal side effects associated with other antipsychotics. Despite its clear benefit in these areas, its use has been associated with a serious, and sometimes life-threatening, risk for agranulocytosis. Effective white blood cell monitoring systems have been developed by Novartis affiliates across the world to ensure its safe use and to meet local health standards. The goals of the monitoring programs include: (1) weekly white blood cell monitoring during the initial months of therapy for early detection of severe leukopenia; (2) immediate discontinuation of clozapine if severe leukopenia is observed; (3) exclusion from reexposure to clozapine if a patient experiences clozapine-induced agranulocytosis; and (4) early cessation of treatment if hematologic guidelines are not followed (“no blood, no drug” policy). Together, these systems have demonstrated a worldwide reduction in the observed rate of agranulocytosis and in fatalities related to the emergence of agranulocytosis when rigorous monitoring systems are in place.

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Clinical studies from the early 1970s indicate that clozapine showed great promise in becoming the treatment of choice for a broad spectrum of psychotic disorders. Ten years ago, the results of the U.S. Clozaril Multicenter Study, a double-blind comparison with chlorpromazine, indicated that clozapine produced a significantly greater improvement on the Brief Psychiatric Rating Scale, Clinical Global Impressions scale, and Nurses’ Observation Scale for Inpatient Evaluation in a very well-defined group of treatment-resistant patients¹; this improvement included negative as well as positive symptom areas. More recently, clozapine has been shown to have a beneficial effect on 2 further domains: cognitive function^{2,3} and affective symptoms/disorders.⁴ Substantial evidence also exists to support the role of clozapine in treating the violent and/or aggressive patient with schizophrenia⁵ and, ultimately, in reducing the incidence of suicidality.^{6,7} Taken together, these results indicate that clozapine represents the current “gold standard” for the efficacious therapy of treatment-resistant schizophrenia and severe psychotic disorders.

In addition to the proven efficacy, clozapine is found to have a distinctive safety profile. Its use is associated with

only minimal extrapyramidal side effects,⁸ including a near absence of associated parkinsonism, dystonias, and tardive dyskinesia.⁹ This profile has led to clozapine’s recommended use in patients who experience intolerable adverse effects from standard antipsychotic therapies. Clozapine use has also been shown to be accompanied by minimal elevations in plasma prolactin concentrations¹⁰ and a very low incidence of neuroleptic malignant syndrome.

On the other hand, its use has been associated with a number of side effects common to other antipsychotics; these include sedation, tachycardia, hypotension, a dose-related reduction in seizure threshold, and weight gain.¹¹ Other side effects are more uniquely identified with clozapine. Sialorrhea is relatively common but can generally be managed with standard clinical interventions. Of more concern is idiopathic agranulocytosis, which can be life-threatening if undetected and requires more innovative approaches to patient management.^{12,13}

AGRANULOCYTOSIS WITH CLOZAPINE

In the mid-1970s, 17 Finnish patients developed agranulocytosis from a group of 35,000 persons who had received treatment with clozapine. Eight of these patients developed severe infections and died.¹⁴ This unfortunate event prompted an intensive investigation into identifying local factors, either genetic or environmental, that might have explained or predicted these events. However, no clear risk factors have ever been identified,^{15,16} and, to date, it has still not proven possible to characterize and predict which patients will develop agranulocytosis.¹⁷

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Table 1. Algorithm for Management of Agranulocytosis^a

WBC > 3000/mm ³ Decreases in WBC > 3000/mm ³	Patient may initiate therapy with clozapine Repeat WBC and differential
WBC < 3500/mm ³ or ANC > 1500/mm ³	Monitor WBC twice weekly with differential
WBC < 3000/mm ³ or ANC < 1500/mm ³	Interrupt clozapine therapy, daily WBC count with differential, monitor for flu-like symptoms
WBC < 2000/mm ³ or ANC < 1000/mm ³	Interrupt clozapine therapy, daily WBC count with differential, bone marrow aspiration, possible protective isolation; non-rechallengeable UNLESS associated with other drug, chemotherapy

^aData from reference 18, the Clozaril National Registry, and data on file, Novartis. Abbreviations: ANC = absolute neutrophil count, WBC = white blood cell.

Although the general population's white blood cell (WBC) counts fluctuate widely over time, data from patients who experienced agranulocytosis indicate that individuals with leukopenia (a depressed WBC count) are at increased risk of developing agranulocytosis. Indeed, if leukopenia is severe, as many as 50% of these patients subsequently go on to develop agranulocytosis. An algorithm for the management of agranulocytosis is shown in Table 1.

The 1% to 2% incidence of agranulocytosis observed in early clinical trials, in the absence of a highly structured blood monitoring system, resulted in clozapine's use being limited to therapy for treatment-resistant schizophrenia and necessitated the worldwide development of stringent surveillance procedures to ensure its safe use.¹⁹ Slightly different approaches to monitoring have been taken in different countries to meet differing local regulatory requirements, but the general solution has been a "no blood, no drug" policy.

To guarantee compliance with monitoring by health care providers, 4 countries have adopted centralized national blood monitoring systems in addition to requirements for physician-based monitoring of WBC counts. These countries are Australia (where the system is known as the Clozaril Patient Monitoring System [CPMS]), Canada (Clozaril Support and Assistance Network [CSAN]), the United Kingdom (U.K. Clozaril Patient Monitoring Service [CPMS]), and the United States (Clozaril National Registry [CNR]). All 4 systems are based upon the same key principles that govern the continued prescription of the medication:

- weekly WBC monitoring during the initial months of treatment with clozapine therapy for early detection of severe leukopenia
- immediate discontinuation of clozapine therapy if severe leukopenia develops
- exclusion from reexposure to treatment with clozapine if a patient experiences documented clozapine-induced agranulocytosis

Table 2. Current U.S. Definitions for Mild, Moderate, and Severe Leukopenia^a

Mild leukopenia WBC 3000–3500/mm ³ ANC ≥ 1500/mm ³	Begin twice-weekly WBC monitoring with differential Clozapine therapy may continue Watch for and treat infections
Moderate leukopenia WBC 2000–3000/mm ³ ANC 1000–1500/mm ³	Discontinue clozapine immediately Institute WBC monitoring every day until WBC count ≥ 3000 Clozapine therapy may be reinstated after normalization of WBC counts Watch for and treat infections
Severe leukopenia WBC < 2000/mm ³ ANC 500–1000/mm ³	Discontinue clozapine immediately Consult with a hematologist Monitor patient daily until WBC and differential counts return to normal (usually about 2 weeks) Treat infections aggressively Clozapine must not be restarted

^aData from reference 18, the Clozaril National Registry, and data on file, Novartis.

- early cessation of treatment in cases where deviation is evident from this monitoring system. This is in accord with the "no blood, no drug" policy.

The Clozaril National Registry

The oldest and largest of these registries is the CNR in the United States. To develop a functional system, terms like *mild leukopenia*, *moderate leukopenia*, *severe leukopenia*, and *agranulocytosis* had to be defined so that they were used consistently across treating centers within the reporting system. These terms were to be used as flags that would trigger ever increasing levels of surveillance and thereby prevent continuation of clozapine therapy if it appeared that the patient was developing agranulocytosis. As indicated above, significant numbers of patients develop temporary leukopenia that is asymptomatic and does not represent a danger to the patients' health. However, with increasingly severe leukopenia, epidemiologic data suggest that the risk for clozapine-induced agranulocytosis increases dramatically. Patients whose WBC count drops to a range of 2000–3000/mm³ have a 4-fold increased risk for developing agranulocytosis (WBC < 500/mm³), and 50% of patients whose WBC count falls into a range of 500–2000/mm³ go on to develop agranulocytosis. In the United States, definitions of *mild*, *moderate*, and *severe* leukopenia have been developed to reflect these risks. Monitoring systems in other countries have developed similar, though not identical definitions.

Table 2 lists the current U.S. definitions for these milestones; the corresponding levels of intervention recommended to prevent leukopenia from developing into frank agranulocytosis are also presented. Mild leukopenia is considered to represent a warning that a patient is at increased risk of agranulocytosis, although it is still acceptable to continue with treatment. However, any subsequent reduction in either WBC or absolute neutrophil count (ANC) necessitates immediate discontinuation of clozapine and even

higher levels of vigilance in terms of WBC monitoring. Severe leukopenia is considered the critical threshold for an afflicted patient to be entered into a related registry (the Clozaril National Non-Rechallenge Masterfile). Because of their unacceptably high risk of developing a life-threatening agranulocytosis, patients are entered into this registry to ensure that the individual will not be prescribed clozapine in the future.

Experience to date with the CNR, as of early May 1998, is that close to 170,000 patients have been exposed to clozapine therapy, of whom 64,000 were actively receiving treatment with the drug. The database exceeded 20 million lines of WBC data from registered patients. At that time, approximately 1800 patients had been judged to fall into the non-rechallengeable category, i.e., WBC counts of less than 2000/mm³. This detailed registry has allowed the number of deaths associated with clozapine use to be carefully tracked. Of patients registered, 680 have died while being treated with clozapine and, of these, only 19 have died as a result of agranulocytosis.

Compliance is a key factor overseen by the registry. Compliance is much more than simply the patient taking his or her medication. In addition, the patient must complete regularly scheduled blood draws and the physician must ensure that the results are reported to the registry. During the early clinical trials program, less than 80% of patient/physician treatment aids were considered to meet these rigorous criteria for compliance. With the advent of the CNR, compliance has reached 99%. Furthermore, the 1% to 2% incidence of agranulocytosis evident before the CNR was established has subsequently been reduced to a rate of 0.38%,^{20,21} a figure that, although still high, approaches the rate seen with other central nervous system agents associated with a low incidence of agranulocytosis.

Risk of Fatality With Agranulocytosis

Clinically, the risk of fatality related to agranulocytosis is far more significant than the simple risk of agranulocytosis. Because the majority of neutropenia that have been detected by the CNR have been asymptomatic, the early exclusion of patients from treatment has meant that patients have had clozapine therapy discontinued before an infection has set in and intensive antibiotic therapy becomes critical. The impact of this preventive action is reflected in a reduced fatality rate among patients developing agranulocytosis.²² The case fatality rate among the initial group of Finnish patients who developed agranulocytosis following treatment with clozapine was 47%, but, with the activity of the monitoring system, the case fatality rate has been reduced to 3%.²⁰ Thus, the CNR has been associated with a reduced risk for agranulocytosis and a subsequent reduced case fatality rate should agranulocytosis occur. In comparison, although the risk of mianserin-induced agranulocytosis is lower and does not require a special monitoring system, it is associated with a 15% risk of fatality.²²

Table 3. Comparable Rates of Agranulocytosis and Fatalities Are Seen With Each of the Centralized Monitoring Systems^a

System	No. Patients Exposed	Agranulocytosis	
		Cases	Fatalities
CPMS (Australia)	6969	46	0
CSAN (Canada)	8414	63	1
CPMS (UK)	15,733	112	2
CNR (US)	172,938	1856	19

^aData from reference 18, the Clozaril National Registry, and data on file, Novartis. Abbreviations: CNR (US) = Clozaril National Registry, CPMS (Australia) = Clozaril Patient Monitoring System, CPMS (UK) = Clozaril Patient Monitoring Service, CSAN (Canada) = Clozaril Support and Assistance Network.

Evaluation of the other 3 centralized monitoring systems (those in Australia, Canada, and the United Kingdom) reveals comparable rates of agranulocytosis and subsequent fatalities (Table 3).

Risk of Agranulocytosis With Increasing Clozapine Exposure

The tracking systems provided by the Novartis registries have permitted determination of whether the risk of developing clozapine-induced agranulocytosis changes with increasing exposure. These databases have permitted determination that the risk of developing agranulocytosis is greatest during the initial 6-month period of exposure to clozapine (860 cases per 100,000 person-years' exposure) than at subsequent timepoints (70 cases/100,000 person-years' exposure during months 7–24; 40 cases/100,000 person-years' exposure for months 25–42; and 20 cases/100,000 person-years' exposure for months 43–66) (data on file, Novartis, 1991–1995). However, even at these subsequent timepoints, the risk of developing agranulocytosis and possible death remains well above that seen in the general population.

DISCUSSION

The reduced incidence of agranulocytosis and associated decreased mortality suggest that at least 130 lives can be saved annually as a result of the careful monitoring that occurs with the patient monitoring systems that Novartis has developed to ensure the safe use of clozapine worldwide.²¹ From this, it is apparent that the added logistical requirements that these systems place upon the patient, physician, pharmacist, and manufacturer have substantially reduced the most serious risks associated with clozapine therapy. Furthermore, data from patient surveys and pharmacoeconomic studies support the conclusions that these systems are cost-effective and are associated with high patient satisfaction, providing safe and successful therapy in patients who would otherwise be inadequately treated as a result of their uncontrolled positive and negative symptoms, cognitive disturbances, and suicidality.

CONCLUSION

In summary, clozapine represents the “gold standard” therapy for treatment-resistant schizophrenia. It is associated with a reduced propensity to induce extrapyramidal side effects and is also considered to be the “gold standard” in this respect. Effective WBC monitoring systems have ensured that clozapine can be used safely and patients can receive the benefits it has to offer despite its association with the serious, and sometimes life-threatening, risk of agranulocytosis.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril, Leponex).

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