

# Reducing Clozapine-Related Morbidity and Mortality: 5 Years of Experience With the Clozaril National Registry

Gilbert Honigfeld, Ph.D., Felix Arellano, M.D., Jitender Sethi, Ph.D.,  
Anthony Bianchini, and Jeffrey Schein, Dr.P.H., M.P.H.

The Clozaril National Registry (CNR) was created to help protect patients from developing potentially fatal agranulocytosis secondary to treatment with the antipsychotic medicine clozapine. The CNR, designed and maintained by the manufacturer of the branded Clozaril (clozapine), has the principal goals of (1) prophylaxis—preventing inappropriate retreatment, and (2) quality assurance—overseeing adherence to a “no blood, no drug” policy. This article reviews the estimated impact of the CNR on clozapine-related morbidity and mortality over the first 5 years of commercial experience in the United States. **Method:** Complete data on leukopenia and agranulocytosis, gathered from the CNR database for the period of 1990–1994, were reviewed and compared with data from the pre-CNR period. **Results:** Use of clozapine in 99,502 patients according to package labeling requirements (distribution of the medicine linked to mandated white blood cell count testing) was associated with a total of 382 cases of agranulocytosis (0.38%) versus an expected cumulative total of 995 cases (based on the pre-CNR rate of 1% to 2%). Based on the expected agranulocytosis rate, up to 149 deaths might have been anticipated. Instead, there were only 12 deaths attributed to complications of agranulocytosis. **Conclusion:** The CNR provides for universal rechallenge protection as well as controlled dispensing of clozapine. It also serves as an early warning system to promote the safe and effective use of clozapine. The CNR includes quality assurance mechanisms designed to enhance compliance. Despite the added logistic requirements this system places upon physician, pharmacist, and manufacturer, the CNR has helped to reduce substantially potential fatal outcomes. The CNR reinforces both patient and treatment system compliance. Based on this favorable experience concerning agranulocytosis and associated fatalities, the Neuropsychopharmacology Advisory Committee to the U.S. Food and Drug Administration has unanimously recommended a reduction in frequency of the white blood cell count testing requirement after 6 months to every 14 days, instead of weekly. Finally, the CNR database containing white blood cell count and demographic data on every patient in the United States who has received the medicine has served as a unique epidemiologic database.

(*J Clin Psychiatry*. 1998;59[suppl 3]:3–7)

About 1 adult in 100 in the United States (approximately 1.5 million) suffers from schizophrenia.<sup>1,2</sup> At least 10% to 20% of these patients are unresponsive to typical antipsychotic pharmacotherapy.<sup>3,4</sup> Another group of patients may respond to antipsychotics but experience dose-limiting extrapyramidal symptoms (EPS) or tardive dyskinesia (TD). A large-scale survey of psychiatric patients treated with conventional antipsychotics found an

overall proportion of TD of 23%.<sup>5</sup> The prevalence of TD was calculated to be about 5% per year of cumulative exposure to the medication for younger patients for at least the first 4 to 5 years; this frequency is probably much higher in older patients.<sup>5</sup> Tardive dyskinesia is a major cause of successful malpractice litigation against psychiatrists.<sup>6</sup> Thus, in those patients who do not respond to conventional antipsychotic therapy or for whom EPS become unacceptable, such treatment is often reduced or voluntarily discontinued by the patient.<sup>3,7</sup>

Clozapine (Clozaril), an atypical, dibenzodiazepine antipsychotic, has been found to offer therapeutic benefits superior to chlorpromazine for a group of hard-to-treat patients: (1) neuroleptic-nonresponsive patients and (2) those potentially sensitive to the adverse effects of neuroleptics.<sup>3,8–12</sup> A pivotal, comparative study in 268 treatment-resistant patients demonstrated the therapeutic superiority of clozapine to chlorpromazine in relieving both positive and negative symptoms. Among patients treated with

*From the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway (Dr. Honigfeld) and Novartis Pharmaceuticals Corporation, East Hanover, N.J. (Drs. Arellano, Sethi, and Schein and Mr. Bianchini). Dr. Arellano is currently at Zeneca Pharmaceuticals, Wilmington, Del.*

*Supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation.*

*Reprint requests to: Gilbert Honigfeld, Ph.D., University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, 675 Hoes Lane, Piscataway, NJ 08844-5635.*

University of Wisconsin

MAR 31 1998

1305 Linden Drive  
Madison, WI 53706

clozapine alone, within 6 weeks 30% were judged to be responders, compared with only 4% of patients treated with chlorpromazine plus benztropine ( $p < .001$ ).<sup>3</sup> Clozapine has also been associated with a near absence of EPS and no documented cases of TD attributed to clozapine alone.<sup>13-17</sup>

Despite these benefits, clozapine use has been limited only to those patients who are resistant to or intolerant of other antipsychotic medications. This policy is based largely on premarketing clinical research and foreign postmarketing experience during the 1970s and early 1980s, which showed that approximately 1% to 2% of treated patients developed agranulocytosis, a potentially fatal complication.<sup>18-25</sup> Bringing these data of the 1970s into closer focus, however, revealed that the condition was reversible and that the risk of death was related to the time and clinical conditions under which the diagnosis of agranulocytosis was made. When clozapine-related agranulocytosis was diagnosed after the onset of infection, as many as 50% of the initially affected patients died. But when their condition was detected by blood test before they developed complications, and the medication was promptly discontinued, no patients with agranulocytosis died.<sup>22</sup> These results suggested that a patient surveillance system providing an early warning of significant decreases in white blood cell count (WBC) could help limit the number and severity of episodes of agranulocytosis.<sup>24,25</sup> Clozapine was approved in 1989 for use in the United States contingent on the manufacturer's implementation of such a surveillance system, the Clozaril National Registry (CNR).

**Clozapine and the risk of agranulocytosis.** Agranulocytosis is defined as an absolute neutrophil count (ANC) below  $500/\text{mm}^3$ .<sup>26</sup> The onset of clozapine-induced agranulocytosis is usually marked by a gradual fall in WBC counts, often over several weeks; rapid WBC drops within 1 week may also occur, but are much less common.<sup>7,27</sup>

Most instances of clozapine-related agranulocytosis occur early in the course of treatment. In a retrospective analysis of 366 agranulocytosis cases between 1973 and 1990, 75% occurred within the first 18 weeks of treatment.<sup>22,23</sup> The peak period of risk for agranulocytosis was found to be during the third month of treatment.<sup>28</sup>

When clozapine therapy is stopped upon identification of marked leukopenia, patients usually recover medically and hematologically within 14 to 24 days and without sequelae. However, rechallenging patients who have experienced clozapine-induced agranulocytosis leads to the redevelopment of the dyscrasia. The onset of the new episode is usually more rapid and more aggressive than the original episode. In 9 patients known to have been rechallenged, the average time to the onset of leukopenia (WBC  $< 3000/\text{mm}^3$ ) or agranulocytosis was 24.4 weeks for the first episode and 14.6 weeks for the second.<sup>29</sup> Such patients should not be exposed to clozapine again, since the risk of a fatal outcome is apparently increased.<sup>7,20,27,30</sup>

It is not possible to predict who will develop agranulocytosis, and the reaction is not dose-related.<sup>30</sup> Although some data have suggested the possibility of genetic predisposition to clozapine-induced agranulocytosis,<sup>31</sup> others have not.<sup>32</sup> It has been suggested that the presence of the alleles HLA-B38, DR4, and DQw3 might be associated with an increased susceptibility to agranulocytosis.<sup>31</sup> However, no reliable genetic markers have yet been identified.

## METHOD

### The Clozaril National Registry: Principles and Requirements

Clozapine is dispensed only through participating treatment systems registered with the CNR. Each treatment system consists of a physician, a pharmacist, and a quality assurance chairperson who commit to work together to implement the 5 major principles of the CNR: rechallenge protection, centralized patient registration, weekly WBC monitoring, limited 7-day distribution of the medication, and quality assurance. Except for rechallenge protection prior to treatment, all active clinical decision-making and patient care responsibility occur at the level of the physicians and pharmacists and their staffs, who together comprise each local Clozaril Treatment System. The specifics of each of the 5 basic functions are spelled out below.

**1. Rechallenge protection.** Screening of all patients through the CNR database prior to initiating clozapine treatment prevents patients from receiving the medicine again if they have a record of ever experiencing clozapine-related agranulocytosis or severe leukopenia/granulocytopenia.

**2. Centralized treatment system and patient registration.** The heart of the CNR is an integrated, computerized, confidential database that is maintained by the manufacturer. All physicians and pharmacists who plan to use clozapine for the benefit of specific patients must agree to abide by the package labeling requirements and register with the CNR. Each patient must be registered with the CNR before clozapine treatment begins. Patients are identified only by their initials, Social Security number (SSN), gender, and date of birth.

**3. Weekly WBC monitoring.** All patients taking clozapine must have a baseline complete blood cell count (CBC) before starting therapy. In order for patients to begin clozapine therapy, their baseline WBC must be above  $3500/\text{mm}^3$ . The WBC is then monitored weekly thereafter as long as they stay on the medicine, and for 4 additional weeks following treatment termination. Continuation of therapy requires that the WBC remain above  $3000/\text{mm}^3$ . If a patient's total WBC is found to be below  $2000/\text{mm}^3$  and/or the granulocyte count is below  $1000/\text{mm}^3$ , clozapine therapy must be discontinued and never reinstated. The CBC and WBC may be conducted by any laboratory of the physician's choice.



expected in patients treated with clozapine over the 5-year period 1990 to 1994. Instead, the actual number of persons who died due to complications from clozapine-related agranulocytosis was 12.<sup>24</sup>

Leukopenia occurred in 2931 of these patients (cumulative incidence, 2.95%). This figure is very similar to that obtained during premarketing clinical research, which was 2.8% of all persons exposed to clozapine. This suggests that the reduced risk of agranulocytosis in patients treated with clozapine was not secondary to a reduction in leukopenia. Rather, it reinforces one of the major rationales of the CNR, that early detection of leukopenia through regular WBC monitoring, combined with prompt discontinuation of treatment in patients whose WBCs fall below 3000/mm<sup>3</sup>, will minimize the further progression to agranulocytosis and the associated risk of death.<sup>24</sup>

The primary goal of the CNR has been to reduce morbidity and mortality associated with agranulocytosis, but additional benefits have also accrued from close patient monitoring.<sup>24</sup> For example, the large, and complete, database of all treated patients facilitates epidemiologic analysis. It has allowed researchers to track WBCs in all patients over time and to accurately calculate death rates and causes of death in this population.

**All-cause mortality.** Schizophrenia is a disorder with an age-related risk of death that is approximately 2 to 2.5 times higher than the risk in the general population,<sup>38-42</sup> largely due to a high suicide rate.<sup>43,44</sup> This translates into a decrease in life expectancy of 21.9% for males and 16.4% for females, for a net loss of 16 years for males and 13 years for females.<sup>45</sup> In a recent epidemiologic analysis of all causes of death in 67,072 registered patients (< 54 years of age) being treated with clozapine at the time of death, Walker et al.<sup>25</sup> found an overall reduction in mortality rates compared with non-clozapine-treated controls. The risk of death from all causes was decreased except respiratory diseases, pulmonary embolism, and cardiac conduction disorder, which were rare. These modest increases were more than compensated for, however, by a major decrease in the rate of suicide that was large enough to reduce the overall death rate to a point approaching the death rate of the general population.<sup>25</sup>

## DISCUSSION

Despite the serious adverse potential represented by agranulocytosis, clozapine is the treatment for patients with chronic schizophrenia who fail to respond optimally to other antipsychotic agents.<sup>3,8-12</sup> Clozapine was approved by the U.S. Food and Drug Administration in 1989 for treatment of these patients, provided the manufacturer implemented an early warning system to minimize the risk of agranulocytosis. The CNR has served that function. Analyses of 5 years of patient data comprising all patients who have received clozapine in the United States since

commercialization confirm that, although the rate of leukopenia remained unchanged at near 3%, the Clozaril National Registry-supported use was associated with far lower than expected agranulocytosis-related morbidity and mortality.<sup>24</sup> Twelve of 99,502 patients treated with clozapine through December 31, 1994, died from infections secondary to agranulocytosis.<sup>24</sup> Previous experience, based on a 1% cumulative incidence of agranulocytosis, would have predicted as many as 149 deaths.<sup>24</sup> On the basis of this favorable experience concerning agranulocytosis and associated fatalities, the Neuropsychopharmacology Advisory Committee to the U.S. Food and Drug Administration has unanimously recommended a reduction in frequency of the white blood cell count testing requirement after 6 months to every 14 days, instead of weekly.

Suicide, which accounts for up to half of all deaths in patients with schizophrenia,<sup>41</sup> decreases dramatically in patients receiving clozapine.<sup>25,46</sup> This finding contrasts with earlier studies in patients receiving other antipsychotics that showed increases in depression and potential suicidality.<sup>47,48</sup> The specific mechanism of clozapine-related suicide reduction is uncertain, but significant reductions in both positive and negative symptomatology are almost certainly involved, as is the associated benefit of clozapine-induced euthymia.<sup>49-51</sup>

The CNR also provides an important mechanism for monitoring and optimizing compliance of both patients and treatment systems. Because patients must present for weekly WBCs before they can receive their medication, it has been suggested that this regular contact may be one factor that contributes to good outcomes. Weekly contact with healthcare professionals might play a preventive role as well, because it permits early intervention in patients who evidence suicidal plans or ideation.<sup>46</sup>

Treatment systems' compliance with the CNR protocol requirements is crucial to the success of clozapine treatment. Treatment systems that do not adhere to CNR monitoring standards can be identified through retrospective analyses; subsequent interventions have proven to be effective in restoring system compliance, thus enhancing patient safety and clinical efficacy. The compliance of physician-pharmacist treatment systems during the first 5 years of the CNR was 97%.<sup>24</sup> This contrasts with the situation during the 1970s, before the benefits of close WBC count monitoring were appreciated, when the frequency of WBC monitoring was estimated to be 30% to 45% and was associated initially with agranulocytosis mortality of up to 50%.<sup>19,24</sup>

The CNR provides a system for universal rechallenge protection as well as controlled dispensing of clozapine. The CNR serves as an early warning system to promote the safe and effective use of clozapine. It also includes quality assurance mechanisms designed to enhance compliance. Despite the logistic requirements that this system



places upon physician, pharmacist, and manufacturer, the CNR has helped substantially in reducing fatal outcomes related to clozapine-induced agranulocytosis. The CNR reinforces both patient and treatment system compliance.

Finally, the CNR database, containing WBC data on every patient in the United States who has received this medicine, serves as a unique epidemiologic database, allowing this kind of precise safety assessment.

*Drug names:* benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril).

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