Effects of the Clozapine National Registry System on Incidence of Deaths Related to Agranulocytosis

♦ Gilbert Honigfeld, Ph.D.

Objective: Clozapine is the only medication distributed in the U.S. through a national patient registry system that provides the medication only if results of patients' weekly blood tests show no evidence of significant white blood cell suppression, an effect that can be fatal if it progresses to advanced agranulocytosis. This study assessed morbidity and mortality related to agranulocytosis during the first five years of the national registry system. *Methods:* Data from the national registry database maintained by the U.S. manufacturer of clozapine was used to determine the level of treating systems' adherence to the mandated program of weekly white blood cell counts, number of instances in which clozapine treatment was denied because of prior determination of white blood cell suppression, and number of cases of agranulocytosis and deaths related to agranulocytosis among treated patients from February 1990, when clozapine was commercially introduced in the U.S., through December 1994. The actual numbers of cases of agranulocytosis and related deaths were compared with expected outcomes based on clinical research done before the drug became available commercially. *Results:* Approximately 97 percent of treating systems had a high overall level of adherence to the registry protocol. In 28 instances, the pretreatment authorization requirement resulted in denial of clozapine; after additional data were considered, 15 of the patients were cleared for treatment. The actual incidences of 382 cases of agranulocytosis and 12 related deaths were lower than the expected 995 cases and 149 deaths. *Conclusions:* The clozapine national registry system fostered early detection of white blood cell suppression, prevented retreatment with clozapine of patients who had previously developed white blood cell suppression, and brought about lower than expected rates of agranulocytosis and associated deaths. (*Psychiatric Services* 47:52–56, 1996)

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In 1990, approximately 5 million persons in the United States suffered from severe mental disorders. Of those, more than half, about 2.5 million had schizophrenia (1). Among persons with schizophrenia, between 10 and 30 percent do not respond adequately to standard antipsychotic agents, because the agents have suboptimal efficacy or intolerable adverse effects (2). Thus between 250,000 and 750,000 treatment-resistant persons with schizophrenia reside in the United States. They represent potential candidates for treatment with clozapine, an atypical antipsychotic medication indicated for the treatment-resistant patient. As of December 31, 1994, a total of 99,502 patients in the U.S. had been exposed to clozapine, and more than half of them remained on the medication at that time.

Increased public interest in clozapine and enhanced familiarity of physicians with the medication make it likely that therapeutic use of clozapine will become more common in the coming years. However, clozapine use is associated with risk of agranulocytosis, a potentially fatal blood disorder that is usually reversible if detected early enough. Limitations in social and medical support networks for persons with severe mental illness underscore the need for procedures to help safeguard this vulnerable patient group from such adverse side effects.

In keeping with general principles developed by the Food and Drug Administration, current procedures for distribution of clozapine stipulate that the medication is available in the U.S. only through treatment systems registered with the national registry developed and maintained by the U.S. manufacturer of clozapine. The purpose of the registry is to enhance patient safety by facilitating early detection of potentially dangerous white blood cell suppression, dispensing the medication only to patients with current blood tests, delineating re-

sponsibilities for patient monitoring, and eliminating as candidates for therapy anyone with a history of clozapine-related white blood cell suppression.

All potential candidates for the medication must be cleared through the national registry to identify persons who have had significant clozapine-related white blood cell suppression in the past and who should not receive the medication again because of markedly increased risk of agranulocytosis. White blood cell counts are normally 5,000 per cubic millimeter or greater. A white blood cell count below 3,500 per cubic millimeter indicates leukopenia, a condition of mild white blood cell suppression that is generally reversible upon interruption of clozapine therapy. Agranulocytosis, a potentially fatal complication, is indicated by a white blood cell count below 2,000 and defined by an absolute neutrophil count below 500 per cubic millimeter. Discontinuation of clozapine is mandatory for patients with agranulocytosis because they are at high risk of death secondary to a wide range of opportunistic infections.

The registry system requires all patients to have a baseline white blood cell count and weekly white blood cell counts throughout treatment with clozapine and for four weeks after treatment ends. The medication is dispensed weekly only to patients for whom data on current white blood cell counts are available. The registry system also outlines the responsibilities of physicians, pharmacies, patients, and the medication's manufacturer and wholesale distributors in ensuring proper use of the medication. Distribution of the medication is limited to registered pharmacies, which agree to follow the "no blood–no drug" guidelines.

Treatment systems that fail to fulfill their obligations to report results of weekly monitoring of patients' white blood cell counts are contacted by national registry staff, who explain the risks of clozapine therapy and the requirements for weekly monitoring. Subsequently, national registry staff follow up with the physicians and pharmacists involved to verify that the problems have been corrected.

This paper discusses clinical practice related to the clozapine national registry system, reports on the incidence of agranulocytosis and agranulocytosis-related deaths from February 1990, when clozapine was first distributed commercially in the U.S., to December 1994, and compares this clinical experience with expectations based on premarket clinical research projections.

This study does not address directly the issue of optimizing the frequency and pattern of white blood cell testing, although the study's prospective analyses of rates of agranulocytosis and related deaths may have some bearing on this issue. The issue of whether formal alterations in the current requirement of weekly blood tests will result in an "acceptable" increase in risk is the focus of separate epidemiologic studies and will not be considered here. This study specifically addressed current quality assurance functions and sought to answer the question of whether the use of a single, national registry of all clozapine users in the United States has enhanced patient safety and contributed to the saving of lives.

Methods

The national registry

All data coming to the clozapine national registry are entered into an integrated, computerized database maintained by the manufacturer. Patients' computer records are established during the initial phone calls made by physicians who are seeking clearance to start a specific patient on clozapine. The records include the patient's identifying code number and initials, the physician's identification, the pharmacy's identification, daily dosage of clozapine in milligrams, and white blood cell test dates and results.

These data are retained permanently, and additional data are added each week. As more than 60,000 patients currently receive clozapine, more than 500,000 separate fields of data are sent to the manufacturer's national registry each week. In addition, separate databases are maintained to track all reported adverse reactions. All data analyzed in this report were drawn from those sources and were provided by the manufacturer.

We used these data to examine two process variables related to functions of the national registry system over the first five years of commercial distribution of the medication: level of adherence to the registry protocol and denial of clinically inappropriate retreatment. We also examined two outcome variables—rate of agranulocytosis and rate of deaths related to agranulocytosis—and compared those rates with the rates that were predicted in analyses conducted before the medication was commercially distributed in the U.S.

Results and discussion

Adherence to registry protocol

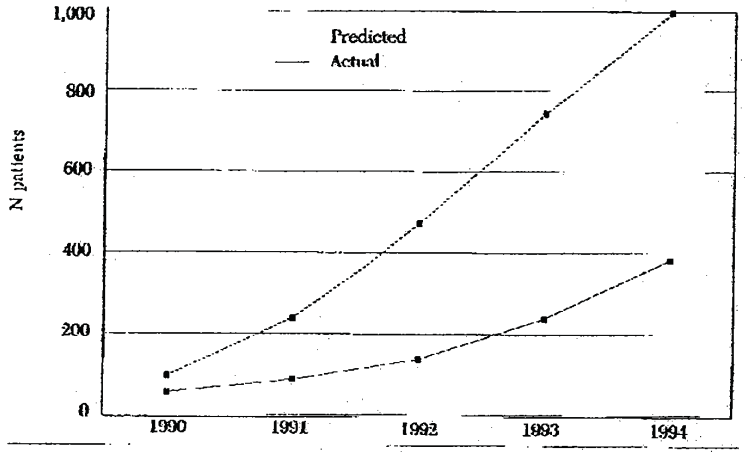
The manufacturer's educational and servicing activities, plus the potential threat of disciplinary action such as deregistration as a clozapine treatment system, appear to have resulted in generally high levels of adherence to weekly monitoring. Over the first five years of commercial distribution of clozapine, more than 97 percent of treating physicians and pharmacists managed their patients on clozapine at high overall levels of adherence to the requirements of the product labeling. The remaining 3 percent have been characterized by varying levels of protocol compliance. National registry data show that a small percentage of treatment systems periodically relax adherence to monitoring guidelines.

Of the more than 10,000 physicians and pharmacists currently involved in dispensing clozapine, about 700 are contacted annually because of poor compliance in reporting data to the national registry. National registry staff institute corrective actions, including education, clinical management training, and intensified review. As new treatment systems are added, and older ones may become large or complacent, this iterative process continues.

Between 1990 and 1992, analyses were performed to determine if corrective actions by national registry staff were associated with improved reporting of white blood cell counts. In March 1992 registry staff identi-

Figure 1

Cumulative number of actual and predicted cases of agranulocytosis among patients receiving clozapine, 1990–1994[1]



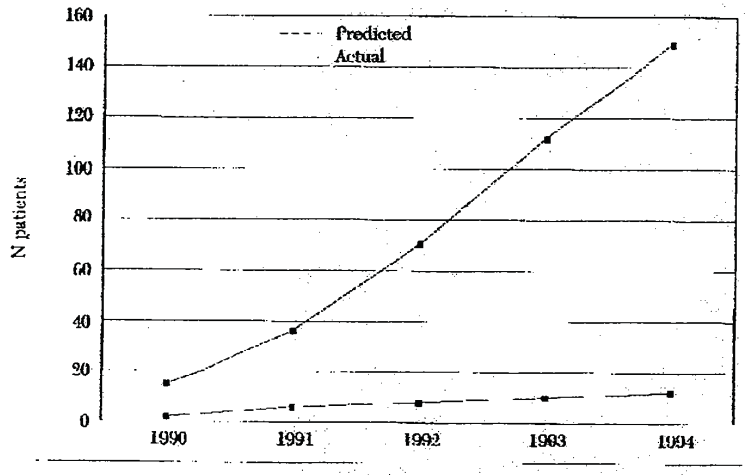
[1] Cumulative numbers of patients receiving clozapine were 9,807 in 1990, 24,112 in 1991, 47,246 in 1992, 74,345 in 1993, and 99,502 in 1994. Predicted number of cases was calculated using a conservative estimate of a 1 percent rate of agranulocytosis, based on premarket clinical research.

fied physicians who had more than six patients for whom more than 10 percent of the required reports of white blood cell counts in the latest three months were missing. From this list, the 100 physicians with the highest percentage of patients for whom more than 10 percent of the reports were missing were identified. At that time, these 100 physicians were responsible for 2,343 patients.

Before the intervention by national registry staff, 58 percent of those patients were missing more than 10 percent of the required records of white blood cell counts. One year later, in April 1993, despite the addition of more than 400 patients to the caseloads of these 100 physicians, for a total of 2,767 patients, the percentage of acceptable reports of white blood cell counts by these physicians had improved to 61 percent.

Figure 2

Cumulative number of actual and predicted deaths related to complications of agranulocytosis among patients receiving clozapine, 1990–1994[1]



[1] Cumulative numbers of patients receiving clozapine were 9,807 in 1990, 24,112 in 1991, 47,246 in 1992, 74,345 in 1993, and 99,502 in 1994. Predicted number of deaths was calculated using conservative estimates of a 1 percent rate of agranulocytosis and a 15 percent rate of associated mortality, based on premarket clinical research.

Denial of retreatment

Patients who have discontinued use of clozapine due to agranulocytosis are at increased risk of developing the reaction again, generally earlier in therapy and in a more aggressive form, if clozapine is reinstituted (3). The national registry clears each potential candidate for clozapine therapy to reduce the chances of reexposure to the medication by persons at increased risk of developing agranulocytosis.

Between February 1990 and December 1994, there were 28 instances in which potential candidates for the medication were denied retreatment. Nine instances involved eight patients who had confirmed histories of white blood cell counts below 2,000 or absolute neutrophil counts below 1,000. The nine instances included two attempts to obtain retreatment clearance for one patient. In four other instances the registry was tested by the manufacturer using identification numbers of non-retreatable patients to assure that the system functioned appropriately. In the other 15 instances, retreatment was denied until closer inspection revealed errors in data; these patients were subsequently cleared for retreatment.

Rate of agranulocytosis

Between February 1990 and December 1994, a total of 99,502 patients were exposed to clozapine in the U.S. and had records of more than one white blood cell count. During the first calendar year in the study period (February through December 1990), 9,807 patients were exposed to clozapine. The cumulative total had increased to 24,112 patients by the end of calendar year 1991, to 47,246 at the end of 1992, to 74,345 at the end of 1993, and to 99,502 by the end of 1994.

Among the total of 99,502 patients

Table 1

Effects of actual and hypothetical rates of compliance in reporting of white blood cell counts on incidence of agranulocytosis and related deaths among patients receiving clozapine

Rate of compliance (%)	Agranulocytosis		Death		N preventable deaths[4]
	Rate (%)[1]	N cases	Rate (%)[2]	N cases	
Actual					
90 to 100[3]	.38	382	3.1	12	—
30 to 45[5]	na	16	50.0	8	—
Hypothetical					
75 to 90	.60	597	5.0	30	18
60 to 75	.80	796	10.0	80	68
45 to 60	1.00	995	15.0	149	137

[1] N cases among 99,502 patients, the cumulative number of patients included in the national registry from February 1990 through December 1994

[2] N deaths among N cases of agranulocytosis

[3] Compared with N deaths at 90 to 100 percent compliance in reporting

[4] Rate among 99,502 cases included in the national registry from February 1990 through December 1994

[5] Rate among patients treated when clozapine was first distributed commercially in Finland in 1975

during the study period, there were 2,931 cases of leukopenia (crude incidence rate of 2.95 percent), 382 cases of agranulocytosis (.38 percent), and 12 deaths associated with agranulocytosis (.012 percent). The rate of leukopenia conforms quite closely to predictions based on premarket clinical research of approximately 2.5 to 3 percent of all persons exposed to clozapine.

However, the crude rate of agranulocytosis during the study period (.38 percent) was less than half that anticipated from premarket research (1 to 2 percent). Figure 1 shows the annual number of expected and actual cases of agranulocytosis over the study period. The expected number of cases was calculated conservatively, using the lower percentage estimate of 1 percent based on the premarket clinical research. Because the rate of leukopenia was consistent in the pre- and postmarket data, the more favorable postmarket findings on agranulocytosis appear to be the result of systematic monitoring, early detection of abnormalities in white blood cell counts, prompt reporting of those counts to the national registry, and prompt discontinuation of clozapine among patients who were at risk for agranulocytosis.

Death rate

Despite intense monitoring, 12 persons died as a result of agranulocytosis-related complications between February 1990 and December 1994. Figure 2 shows the cumulative expected and actual numbers of deaths related to agranulocytosis each calendar year during the study period. The expected death rate assumes a 1 percent rate of agranulocytosis and an associated mortality rate of 15 percent. This rate is consistent with conservative estimates based on experience abroad with clozapine and on published research on imianserin, an antidepressant that has leukopenia as a potential adverse effect (4,5).

The difference between the predicted and actual cumulative death rates—149 predicted deaths compared with 12 actual deaths—suggests the benefits of rigorous patient monitoring. These data show that current medical practice and monitoring procedures have contributed substantially toward saving the lives of many patients who require clozapine therapy.

Table 1 shows how patient survival might have been affected over the study period if monitoring had been less rigorous. Actual clinical experience in the U.S. from February 1990 through December 1994 showed 90 to 100 percent compliance with reporting of white blood cell counts. In that context, patients with agranulocytosis had an overall risk of fatal complications of 3.1 percent (12 deaths among 382 cases of agranulocytosis).

At the other extreme are the initial findings on this topic from Finland in 1975–1976, where a 50 percent rate of mortality emerged among patients who developed agranulocytosis (eight deaths among 16 cases of agranulocytosis). Rates of white blood cell monitoring were estimated to be 30 to 45 percent. The outdated medical and monitoring conditions existing at that time clearly no longer apply, given the heightened awareness of clozapine and its therapeutic and adverse effects. However, between the current U.S. experience, representing the highest level of monitoring, and the early Finnish experience, one can interpolate intermediate scenarios of adequate, fair, or poor levels of monitoring and the associated risks of fatal complications of agranulocytosis.

Table 2

Prospective analysis of effects of rates of compliance in reporting of white blood cell counts on incidence of agranulocytosis and related deaths among 20,000 new patients receiving clozapine over a one-year period

Rate of compliance (%)	Agranulocytosis		Optimistic scenario[1]		Realistic scenario[2]		
	Rate (%)	N	N deaths	N preventable deaths[3]	Rate of death (%)	N deaths	N preventable deaths[3]
90 to 100	.38	76	2	0	3.1	2	0
75 to 90	.60	120	4	2	5.0	6	4
60 to 75	.80	160	5	3	10.0	16	14
45 to 60	1.00	200	6	4	15.0	30	28

[1] Assumes a 3.1 percent rate of death among cases of agranulocytosis, regardless of the number of cases at various levels of compliance

[2] Assumes rate of death among cases of agranulocytosis increases as number of cases increases with decreased levels of compliance

[3] Compared with two deaths at 90 to 100 percent compliance in reporting

For example, a rate of compliance with white blood cell monitoring of 75 to 90 percent would be associated with a risk of fatal complications of an estimated 5 percent among patients who developed agranulocytosis, a monitoring rate of 60 to 75 percent with an estimated 10 percent rate of fatal complications, and a monitoring rate of 45 to 60 percent with an estimated 15 percent rate of fatal complications, the level recently reported for deaths related to agranulocytosis associated with mianserin (4). Thus if monitoring standards in the U.S. had been less stringent between 1990 and 1994, between 30 and 149 deaths might have occurred, instead of the 12 deaths that actually occurred.

Prospective analyses

Based on conservative projections of current rates of access to clozapine, at least 20,000 Americans per year are likely to be newly exposed to clozapine in the coming years. If these patients are treated under current monitoring conditions, about 76 patients (.38 percent) are likely to develop agranulocytosis, and two patients are likely to die of complications of agranulocytosis (3.1 percent among agranulocytosis cases) in each annual cohort.

Given these rates, what would happen if standards for monitoring were lowered? Two principal scenarios, whose rates are shown in Table 2, can be considered. An optimistic scenario presumes that medical practice has advanced enough that most cases of agranulocytosis, including symptomatic cases, can be arrested without fatal complications. Thus if one assumes that adequacy of monitoring has no bearing on fatal outcomes, two deaths could be anticipated among the next 20,000 new clozapine patients if monitoring compliance remains at current levels. If the rate of compliance drops, one will likely see an increase in the rate of agranulocytosis and an additional two to four deaths.

The second, more realistic scenario assumes that early detection and continued vigilance exert a favorable impact on the rate of agranulocytosis and the rate of fatalities. In this scenario, a wider range of outcomes can be projected, and substantially poorer outcomes are likely. For example, the estimated risk of agranulocytosis would range from .38 to 1 percent and the rate of fatalities from 5 to 15 percent. The projections shown in Table 2 suggest that if monitoring deteriorates from current levels, between four and 28 additional deaths may occur among each annual cohort of new patients.

Conclusions

In the first five years of commercial distribution of clozapine in the U.S., the national clozapine registry system appears to have contributed to reducing mortality related to complications of agranulocytosis substantially below projected rates derived from premarket data. The rigorous safeguards in place to maximize the opportunities for early detection of white blood cell suppression have been associated with favorable outcomes in rates of both agranulocytosis and fatal complications. Decreased vigilance would likely be associated with an increase in otherwise preventable deaths. ♦

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