

Clozapine Eligibility Among State Hospital Patients

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Abstract

Connecticut State Hospital's entire resident population ($n = 1,300$) was screened on an arbitrary target day to determine eligibility for clozapine. Sixty percent of 803 patients with schizophrenia or schizoaffective disorder diagnoses met Food and Drug Administration (FDA)-approved criteria for clozapine use as judged by review of past medication trial records and by the responsible physician. Eighty-eight percent of these patients were medically cleared, and of those cleared, 63 percent agreed to clozapine treatment. Of the patients who began a clozapine trial, 76 percent were still taking the drug 12 months later. Preliminary findings from a randomized trial of clozapine versus usual care ($n = 227$) indicate that discharge rates associated with clozapine and usual care do not differ. Once discharged, however, patients assigned to clozapine are less likely to be readmitted. Hence, clozapine may be more cost-effective than usual care. However, before savings can be realized, State governments will have to make up-front investments of approximately \$140 million simply to give patients hospitalized on a single day a year's access to clozapine.

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Clozapine is an effective but expensive treatment for schizophrenia, indicated for patients who have not responded adequately to standard antipsychotic drugs (Meltzer 1992). A year's supply of clozapine tablets plus the required

weekly blood monitoring to detect agranulocytosis costs \$5,000 to \$10,000 per patient, making clozapine one of today's most expensive antipsychotic drug treatments. Giving all eligible individuals in the United States a clozapine trial could cost as much as \$3.6 billion annually (Meltzer et al. 1990), although authors of such projections usually note that comprehensive cost-effectiveness studies are still needed.

Treatment-refractory schizophrenia patients typically are treated at State hospitals, community mental health centers, and other public facilities. The long duration of their illness's active phases frequently results in poverty, disability, and lengthy hospital stays for those who do not respond favorably to traditional antipsychotic medications.

Clozapine has been shown to be effective for 30 percent or more of such patients after only 6 weeks of treatment (Kane et al. 1988). Response rates after 3 months of treatment have been shown to be even higher (Meltzer 1992). Clozapine's expense raises questions about its cost-effectiveness, particularly for patients in State hospitals.

The Connecticut Department of Mental Health and Addiction Services (CDMHAS) has undertaken a study of the costs and effectiveness of clozapine for severely ill patients in the State's mental health system. Because the funds initially appropriated by the legis-

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lature for clozapine were less than what was needed to treat all eligible patients, CDMHAS implemented a pilot project in which qualified patients were randomly assigned to either clozapine or usual care, as an equitable way to allocate the limited number of funded clozapine "slots." Study participants are being followed for 2 years to determine clinical course, type of services required, and cost of care. This report estimates the size and character of the target group (State hospital patients diagnosed with schizophrenia), the proportion of this group eligible for clozapine, and the number of patients who will accept clozapine once it is offered. It also provides preliminary outcome data on trial duration and on discharge and readmission rates.

Two groups of investigators have reported on epidemiological assessments of clozapine treatment eligibility. Terkelsen and Grosser (1990) constructed retrospective estimates based on three large-scale surveys, conducted in 1987 and 1988, of patients in New York State. The FDA-approved package insert criteria were not used. Instead, criteria approximated the "compassionate use" protocol followed for clozapine before its market release. The protocol criteria were more restrictive than the package insert criteria. Furthermore, the effectiveness of prior medication trials, a key criterion, could not be applied to the data available. Also, exclusion criteria were related more to predicting whether clinicians would select the patient for clozapine treatment than to eligibility by objective criteria. The authors did not attempt to estimate the number of patients who would consent to clozapine

treatment. Only 18 percent of inpatients and 24 percent of outpatients with schizophrenia were estimated to be eligible for clozapine treatment. The differences in criteria from current standards render these estimates of eligibility outdated.

Juarez-Reyes et al. (1995) used a broad interpretation of the FDA criteria to estimate clozapine eligibility rates among clients in a county mental health system in California. They drew a stratified, random cluster sample of 293 persons with schizophrenia from all clients (including State hospital patients) served by the mental health system during 1991. Eligibility data were abstracted from clinical records. Eligible patients were diagnosed with schizophrenia or schizoaffective disorder, were age 16 or older, had two prior neuroleptic trials of at least 600 mg/day chlorpromazine equivalence for at least 4 weeks, or tardive dyskinesia (TD), and had a Global Assessment of Functioning score (American Psychiatric Association 1987) less than 61. No contraindications beyond those mentioned in the package insert were considered. The population eligibility estimate for these broad criteria was 42.9 ± 5.9 percent. Eligibility was reduced to 12.9 ± 2.7 percent by imposing more stringent criteria similar to those used in the Kane et al. (1988) multicenter trial, which was the basis for marketing clozapine in the United States. No estimate could be made of whether the patient would pass final medical clearance or agree to clozapine treatment if it was offered. Therefore, an estimate of the percentage of patients who could actually be treated with clozapine would be lower. The authors did not esti-

mate eligibility separately for State hospital patients.

Two groups have reported preliminary information on the cost-effectiveness of clozapine not specifically relevant to State hospital patients (Honigfeld and Patin 1990; Revicki et al. 1990, 1991; Meltzer et al. 1993). These studies indicate that substantial cost savings may be possible for individuals who respond positively to clozapine. Serious limitations in the designs of these two studies have been discussed in the literature (Frank 1991; Goldman 1991; Revicki et al. 1991; Essock 1995; Rosenheck et al. 1995; Schiller and Hargreaves 1995).

Several authors have reported clozapine outcomes for State hospital patients specifically. These reports have focused on reductions in hospital days and in aggressive behavior. None are controlled trials or even involve comparison groups except where comparisons are made to patients who discontinued clozapine.

Reid et al. (1994) examined 172 patients who had started clozapine in Texas State hospitals and had remained on it for at least 1.75 years. Inpatient (bed) use after start of clozapine was compared to use in the two 6-month periods just prior to start of clozapine. Statistical tests are reported only in comparison with the second baseline period with the higher bed use, possibly reflecting a factor affecting patient selection for clozapine treatment and therefore potentially biasing the statistical tests toward significance. The first 9 months after start of clozapine showed no significant reduction in bed use, but each subsequent 6-month period showed significantly lower use than at baseline.

At \$250 per bed day, the decrease in bed use expenditure was estimated to be \$33,000 to \$50,250 per patient per year. As in any mirror-image study, the question is whether the observed reductions can be attributed to clozapine. The authors were appropriately cautious in pointing out the factors that prevented precise estimates of cost savings, including the lack of information on cost for patients who began but did not continue clozapine and the costs of non-hospital services. Reid et al. (1994) did not report rates of first discharge or readmission following the start of clozapine, so their findings cannot be directly compared to the preliminary results reported in the present article.

Wilson (1992) and Wilson and Claussen (1994) reviewed medical records 6 months before clozapine treatment and 18 months after of the first 100 patients to begin the treatment at a State hospital in Oregon. A strength of this mirror-image study is that monthly time trends are reported on many variables. Thus, the preclozapine time trends help portray the extent to which patients may have been experiencing extreme symptoms and could therefore be expected to return to their usual course regardless of treatment. The authors examined the number of patients in seclusion and the average number of seclusion hours, the number of patients showing violent episodes and the number of episodes, and the mean hospital privilege level. All showed worsening spikes just before clozapine treatment. Still, outcomes on these variables show average improvement trends that exceed pre-spike levels, although significance tests are not reported. Using privilege level as a global

outcome, the authors reported that 37 percent of patients showed no change or worsening, 18 percent showed moderate improvement that reached a plateau at 6 months, and 45 percent showed significant improvement with a privilege level increase in the first 6 months and gradual further improvement approaching the highest privilege levels over the subsequent 12 months. At 1 year, 38 percent had left the hospital, and at 18 months 47 percent had left and 42 percent were still out. By 18 months, 81 percent of the patients were still receiving clozapine. Of the 38 percent discharged within 1 year, 13 percent returned within 6 months. While these trends are suggestive, the mirror-image design prevents one from concluding that improvement was an effect of clozapine treatment.

Dennis et al. (1993) (extending a preliminary report by Chiles et al. 1994) described outcomes for patients given a clozapine trial in a State hospital in Washington. Patients were followed from 12 weeks before start of clozapine to 76 to 104 weeks after start. At 1 year, 92 patients (82%) remained on clozapine and 45 (40%) had left the hospital. Virtually all the discharged patients had remained on clozapine. At 2 years, 89 patients (79%) remained on clozapine and 71 (63%) had left the hospital. Of the 71 who left, only 4 had been rehospitalized by the end of followup. Community exposure varied from 4 to 98 weeks for discharged patients at the end of followup and averaged about 63 weeks—a rehospitalization rate of less than 4 percent per year.

In summary, there has been no systematic estimate of the rate of

clozapine eligibility among State hospital patients and only uncontrolled analyses of discharge and readmission rates among State hospital patients started on clozapine. These uncontrolled studies suggest that initial discharge rates do not show much advantage for clozapine during the first year of treatment, but that 6-month readmission rates for the subset of patients discharged on clozapine are very low.

Methods

Setting. Patients from each of Connecticut's three large State psychiatric hospitals were eligible for the study. In 1991, Connecticut used 50 public psychiatric beds per 100,000 population, compared to the national average of 41 per 100,000 in 1990, the most recent year for which data are available (National Association of State Mental Health Program Directors, personal communication, September 1995). At initial screening for clozapine eligibility on February 28, 1991, these hospitals had a total of 1,300 patients. The median length of stay of these 1,300 patients was 2.6 years, in comparison with a median length of stay of only 0.2 years for people discharged during fiscal year 1991. Like many State hospitals, these hospitals treat long-term residents among whom discharges are relatively rare, as well as patients admitted for shorter stays. While the eligibility phase of this study included all State hospital patients regardless of length of stay, the randomized trial that followed focused on those who had been held longest in restrictive settings and who consumed the most State hospital resources.

Eligibility Criteria. The FDA has approved clozapine for use with "... severely ill schizophrenia patients at least 16 years old who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment." (Sandoz Pharmaceuticals Corporation 1991). CDMHAS interpreted the diagnosis of schizophrenia to include anyone with a current clinical diagnosis of schizophrenia or schizoaffective disorder. We operationalized the required "courses of standard antipsychotic drug treatment" as at least two adequate trials on different antipsychotic medications, at least one of which was a non-phenothiazine. An adequate trial was defined as one in which treatment lasted at least 6 weeks at a dose equivalent to 1,000 mg/day chlorpromazine (dosage equivalency table available on request) or one resulting in side effects such as TD or neuroleptic malignant syndrome. Patients hospitalized because of schizophrenia may obtain substantial relief from neuroleptics yet have ongoing symptoms that keep them hospitalized. CDMHAS considered patients who remained ill enough to be hospitalized to have shown unacceptable responses and, therefore, to be candidates for clozapine. While any person hospitalized because of schizophrenia is considered to be "severely ill," additional criteria were applied to ensure that clozapine was available for those most in need. Upon entry in the randomized trial, a patient must have been a State psychiatric hospital inpatient for at least 4 months, with a total hospitalization (in any institution) of at least 24 months for the preceding 5 years. Exclusion criteria consisted of medical

contraindications to clozapine (e.g., a history of severe, clozapine-induced leukopenia, a current pregnancy).

The survey we used to identify inpatients who met the eligibility criteria forms the core of the findings reported here. A screening form eliciting information from the hospital's information system, patient records, and the treating physician was completed for each patient with a qualifying diagnosis. Patients were then categorized as "potentially qualified," "not qualified," or "does not now qualify but may later" (e.g., a pregnant patient, one who had not yet completed two adequate neuroleptic trials). This phase of the study was designed to use clinicians' time economically; no other eligibility documentation and no discussions with the patient were requested up to this point.

Patients who met the initial eligibility criteria were invited to be in the study unless they were already known to have a medical contraindication to clozapine. Patients themselves were invited to be in the study if they were competent to make this decision. Consent for patients considered incompetent to give it was sought from substitutes (conservators, guardians, family members). Patients were considered competent if their treating psychiatrist answered yes to the following questions:

1. Is the patient aware of the potential danger associated with clozapine?
2. Is the patient aware of the required weekly venipuncture when taking clozapine?
3. Does the patient know why he or she is being asked to participate?

4. Does the patient understand that, if he or she takes clozapine, information about him/her (initials, social security number, clozapine dosages, results of blood work) will be entered in a national registry?

5. Does the patient know that at present CDMHAS dispenses clozapine only to participants in the study?

Patients and substitutes who initially declined study participation were approached again by the treating psychiatrist. If the person still declined, a final offer was made later by another member of the treatment team. Consenting patients then went through the medical clearance process. Once cleared, they were randomly assigned to the experimental (clozapine) or control (usual care) group. By August 1992, when the legislature increased funding for clozapine and rationing was discontinued, 227 patients were participating in the study.

Results

The screening results allowed identification of factors important in determining clozapine eligibility. Nearly two-thirds of the 1,300 adults in residence on February 28, 1991, in Connecticut's State psychiatric hospitals had a diagnosis of schizophrenia or schizoaffective disorder (table 1). Because they were hospitalized, all of these individuals were presumed to meet the FDA criterion of being severely ill. Of the 803 individuals with a qualifying diagnosis on initial screening, 483 (60%) met the FDA requirement of either lack of response to two adequate treatment trials ($n = 392$) or unaccept-

Table 1. Number of patients remaining in the pool of patients eligible for clozapine after application of successive eligibility criteria

Category ¹	<i>n</i>	Total census %	Those with qualifying diagnosis %	Preceding category %	Male %
Census on 2/28/91 (all 18 years or older)	1,300	100	—	—	64
Qualifying diagnosis	803	62	100	62	64
No TD documented	730	56	91	91	65
Had ≥ 1 adequate trial	608	47	76	83	64
Had ≥ 2 adequate trials	442	34	55	73	61
Of 2 adequate trials, at least 1 was nonphenothiazine	410	32	51	93	60
Met FDA requirements (TD or 2 adequate trials without adequate response, at least one nonphenothiazine)	483	37	60	—	60

Note.—Data are for patients in residence in Connecticut's three large psychiatric hospitals as of February 28, 1991, and give their status as of that date. FDA = Food and Drug Administration; TD = tardive dyskinesia

¹Each group except "FDA" is a subset of the preceding row.

able side effects with conventional neuroleptics ($n = 91$). Of the 91 individuals who had demonstrated unacceptable side effects to current neuroleptics, 73 had documented TD, and 18 had demonstrated intolerance to trials of conventional neuroleptics for other reasons (typically, these individuals were still receiving neuroleptics, but not at dosages high enough to meet the criterion for an adequate trial). Women were significantly more likely than men to meet the FDA criteria: 62 percent of the 289 women with a qualifying diagnosis met the FDA criteria, compared to 56 percent of the 514 men ($\chi^2 = 9.17$, $df = 1$, $p < 0.01$). Women were more likely than men to have had a second adequate trial ($\chi^2 = 6.13$, $df = 1$, $p < 0.02$) and to have had an adequate trial with a nonphenothiazine ($\chi^2 = 4.32$, $df = 1$, $p < 0.05$). This may not be a gender disparity per se, but may reflect the fact that women in the sample appear to have been, on average, more severely ill than

men (i.e., they were less likely than men to be found competent to give informed consent to be in the study), as well as the fact that more severely ill patients were more likely to have had multiple adequate medication trials. Of the 483 individuals meeting the FDA criteria, 449 (93%) met the CDMHAS severity requirements regarding total days of hospitalization; hence, relatively few patients were excluded from eligibility for the randomized trial for this reason.

Figure 1 represents a "snapshot" of patients in residence on February 28, 1991. Shown are the numbers of patients eventually passing each stage of the competency, consent, and medical clearance process. The chief psychiatrists on each ward were given lists of all their patients who met the initial eligibility criteria (i.e., FDA criteria plus CDMHAS length-of-stay criteria) and consent materials to be completed for each of these patients. Of the 523 patients who

met the initial eligibility criteria on February 28, 1991, or some time thereafter, 40 (8%) had a medical contraindication to clozapine and did not enter the consent process. Beginning in June 1991 and continuing until recruitment ended in August 1992, 368 of the remaining 483 patients (76%) were invited to be in the study. The reasons for not being invited included discharge ($n = 62$), end of recruitment ($n = 39$), diagnosis no longer schizophrenia ($n = 7$), death ($n = 4$), response to current medications ($n = 2$), and receipt of clozapine via a compassionate use program ($n = 1$). Of the 368 patients in residence on February 28, 1991, who were eligible for and asked to be in the study, 276 (75%) were found competent to make the decision. Eighty-two percent of the 241 men but only 62 percent of the 127 women approached were found competent to make this decision ($\chi^2 = 16.92$, $df = 1$, $p < 0.001$), again suggesting that the women patients, on average, were

Figure 1. Patients in residence in any Connecticut State hospital on February 28, 1991, who met both FDA and CDMHAS eligibility criteria

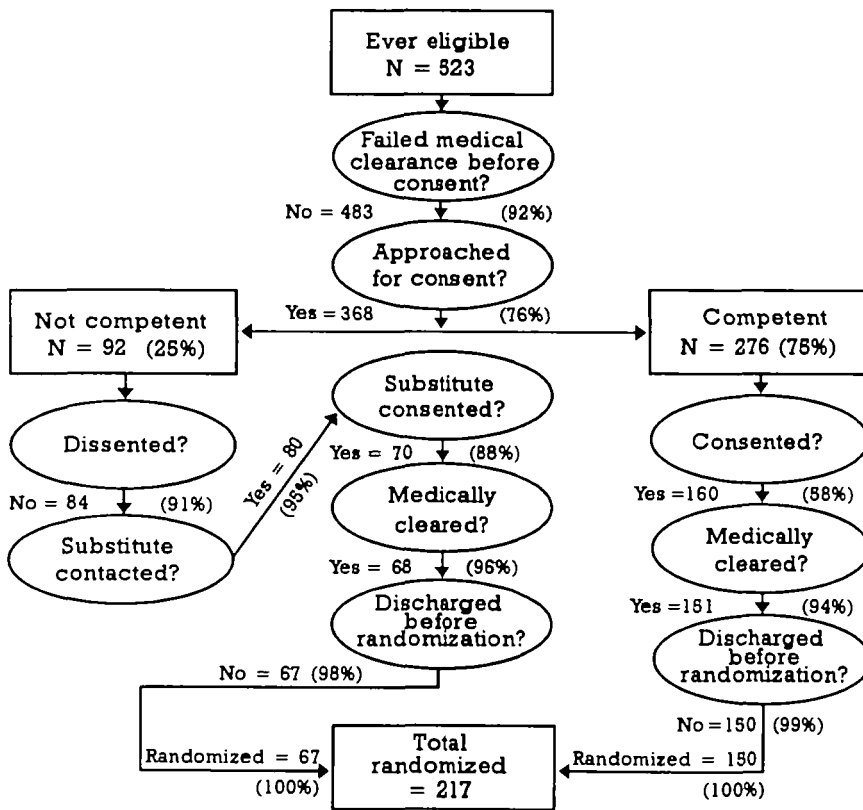


Chart shows numbers of patients eventually passing each stage of the competency, consent, medical clearance, and randomization process. FDA = Food and Drug Administration; CDMHAS = Connecticut Department of Mental Health and Addiction Services.

more severely ill than the men.

Eight patients not competent to give consent stated that they did not want to be in the study, and no consent from a substitute was sought for them. A conservator, guardian, or family member was asked for consent on the patient's behalf for 80 of the remaining 84 assenting but noncompetent patients. Seventy (88%) of these substitutes gave consent. In contrast, of the 276 patients judged compe-

tent to consent, only 160 (58%) agreed to enter the study. Hence, patients were significantly less likely than substitutes to consent to participate ($\chi^2 = 53.3, df = 1, p < 0.001$).

Using duration of current hospitalization as a proxy for severity of illness, we examined the relationships among competency, gender, and agreement to be in the study with severity of illness for the 368 individuals approached for

consent (three-way analysis of variance [ANOVA] with factors of competency status, consent status, and gender). The only significant effect was that incompetent patients were more severely ill than competent patients (mean duration of current hospitalization = 12.1 vs. 7.4 years; $F = 25.85, df = 1,360, p < 0.001$). We also examined how patient age varied with competency status, agreement to be in the study, and gender (three-way ANOVA with factors of competency status, consent status, and gender). Each of the main effects but none of the interactions reached significance. Women in this group were significantly older than men (mean age = 45.3 vs. 41.1 years, respectively; $F = 8.44, df = 1,360, p < 0.004$). Patients judged incompetent were older than competent patients (mean age = 45.9 vs. 41.5 years, respectively; $F = 8.85, df = 1,360, p < 0.003$). Likewise, patients who did not consent (either directly or by substitute) were older than those who did (mean age = 43.9 vs. 41.8 years, respectively; $F = 6.69, df = 1,360, p < 0.01$).

Of the 230 patients who passed the consent process, 219 (95%) received medical clearance for clozapine. Patients most commonly failed to receive clearance because of severe cardiac disease or debilitated physical state, a need for concurrent drugs that could suppress bone marrow function, a history of blood dyscrasia, and the presence of a seizure disorder well controlled only by medications contraindicated for use with clozapine (e.g., carbamazepine). Patients were deemed to have failed medical clearance, and thus denied access to clozapine, only when the hospital's clozapine project director

and the commissioner's psychopharmacology consultant also agreed that a medical contraindication existed. So that we could mimic real hospital practice as closely as possible, our consent estimates included these patients who failed medical clearance after the consent process. Outside of a research setting, individuals would not undergo medical procedures for final medical clearance before agreeing to treatment. Hence, we also spared patients the inconvenience, and hospitals the expense, of procedures associated with medical clearance unless the patient agreed to a possible trial on clozapine.

These data characterize the patients who were potentially eligible to receive clozapine on a given date. The pool of potentially eligible patients in a hospital is always in flux due to admissions, discharges, and changes in eligibility. To determine whether the likelihood of patients' accepting a trial on clozapine changed as more patients tried the drug (and as they had the opportunity to observe the effects of treatment), we examined the acceptance rate over time (ANOVA with factors of competency status and time). The likelihood of consenting to the study (both by patients and by substitutes) did not vary significantly during the enrollment period.

The group of patients who were not eligible for a clozapine trial because they had not had two adequate trials on conventional neuroleptics is of particular interest for two reasons: (1) the rate at which they complete—and their response to—subsequent trials influences projections of the number of patients eligible for clozapine in the future, and (2) monitoring the

subsequent treatment given these patients is a way to identify potential problems in quality of care. On February 28, 1991, 320 inpatients with a qualifying diagnosis and without documentation of TD, using the definitions described above, had not had two adequate trials on conventional neuroleptics (table 1). When clozapine rationing ended 18 months later, 131 patients without adequate drug trials remaining from the February 28 cohort were still hospitalized and potentially appropriate for clozapine. During that 18-month period, however, only 38 of these individuals (29%) had received the additional neuroleptic trial(s) necessary to meet FDA eligibility criteria.

To estimate the number of patients eligible for clozapine per 1,000 occupied State hospital beds, we included both the 483 patients who met the FDA criteria at the time of the initial survey and the 55 in residence at the time of the survey but not eligible until a later date. Using the methods of Fleiss (1981) to compute 95 percent confidence intervals, we estimated that 414 ± 27 individuals per 1,000 occupied beds ($41.4\% \pm 2.7\%$) are potentially eligible for a clozapine trial.

Preliminary Findings of a Randomized Trial. This report focuses on eligibility for clozapine. However, we can report preliminary information on trial duration, discharge rates, and rehospitalization rates for 227 patients randomly assigned to clozapine or usual care. One hundred thirty-eight study participants were assigned to clozapine and 89 to usual care using an unbalanced randomization. These patients were followed for 24 months. The mean

age of individuals assigned to clozapine or to usual care was 42 (standard deviation [SD] = 12 years) and 40 (SD = 11 years), respectively. Sixty percent of the individuals assigned to clozapine and 61 percent of the individuals assigned to usual care were male. The mean length of stay for individuals assigned to clozapine or to usual care was 8.5 years (SD = 8.2) and 8.2 years (SD = 7.7), respectively. The mean age at first hospitalization for the clozapine and usual care groups was 20.1 (SD = 5.5 years) and 18.9 (SD = 4.4 years), respectively.

During the controlled trial, CDMHAS left the decision about when to terminate a trial to the prescribing physician and the patient. Life table analyses of the 136 patients randomized to the clozapine condition who eventually began a clozapine trial indicate that 75 percent of patients who begin such a trial will still be taking clozapine 1 year later and that 64 percent will still be taking clozapine 2 years later. Of the 138 study participants randomly assigned to the clozapine condition, 136 began a clozapine trial during the 2-year study period, and 46 of these discontinued clozapine within this period. The most common reasons for termination were agranulocytosis ($n = 4$), other low white blood cell counts ($n = 4$), hypotension ($n = 4$), other cardiac problems ($n = 4$), other medical problems ($n = 4$), poor clinical response in the absence of medical problems ($n = 7$), poor clinical response plus medical problems contributing to the discontinuation of clozapine ($n = 8$; hypotension = 3, seizures = 2, sedation = 1, other = 2), and patient/family preference ($n = 11$). The two individuals who

were randomly assigned to clozapine who did not begin a clozapine trial within the 24-month study period each had medical complications that arose before the study. One patient had organic problems dating from the time of a lobotomy; the other had mild leukopenia. These problems were not judged severe enough for the patients to fail the hospitalwide medical clearance process; rather, their treating psychiatrists opted not to begin clozapine trials once permission to begin had been granted. Had the treating psychiatrists made their objections known before the consent process, these two patients would have been added to the "failed medical clearance prior to consent" category.

Mean and median clozapine dosages were 486 and 517 mg/day, respectively. The mean and median peak clozapine dosages were 669 and 700 mg/day, respectively. Table 2 shows the frequency with which study participants in the clozapine condition received various ancillary medications. For subjects in the usual care condition, the mean and median chlorpromazine equivalents were 1,386 and 1,191 mg/day, respectively. The mean and median peak chlorpromazine equivalents for these subjects were 2,009 and 2,000 mg/day, respectively (equivalence tables are available on request).

The 1-year discharge rates were 27 percent ($n = 37$ of 138) and 30 percent ($n = 26$ of 89) for the clozapine and control groups respectively, a nonsignificant difference. Once discharged, however, individuals originally assigned to the clozapine group were significantly less likely to be readmitted in the first 6 months following discharge: 3 percent of the

Table 2. Percentage of study participants receiving ancillary medication as a function of time on clozapine for subjects randomly assigned to clozapine who began a clozapine trial

Ancillary medication	Months on clozapine		
	0 ($n = 136$)	12 ($n = 101$)	20 ($n = 92$)
Antianxiety/sedative	66	33	27
Sleeping medication	25	15	11
Lithium	26	16	14
Antipsychotic (p.r.n.)	48	11	12
Antidepressant	10	8	9
Tegretol	10	0	0
Valproic acid	9	4	7

Note.—p.r.n. = as needed.

clozapine group were readmitted ($n = 2$ out of 75 individuals discharged for at least 6 months) versus 29 percent assigned to usual care ($n = 12$ out of 49 individuals discharged for at least 6 months; Wilcoxon (Gehan) comparison = 12.058, $df = 1$, $p < 0.001$).

Discussion

Data from the Connecticut public mental health system may be used to estimate the proportion of State hospital patients who are eligible for a clozapine trial, the number who would agree to a trial, and the number who would pass medical clearance. Our data indicate that, on an arbitrary day in the Connecticut public mental health system (February 28, 1991), 60 percent of inpatients with a qualifying diagnosis satisfied FDA criteria for clozapine use. Data from patients in residence on that "snapshot" date show that 67 percent of the patients with a qualifying diagnosis had met these criteria 18 months later. The percentage of patients who actually are appropri-

ate for a clozapine trial is reduced by eliminating those who have medical contraindications or who decline a trial either directly or via a substitute. Eighty-eight percent of patients who were eligible by diagnostic and treatment-response criteria passed medical clearance, and 63 percent of patients offered an opportunity for a trial accepted it. One might wonder whether this acceptance rate would have been different if patients had simply been offered a clozapine trial rather than random assignment to clozapine or usual care. Data from the Ohio Department of Mental Health indicate that this is not the case. In Ohio, 61 percent of patients offered a clozapine trial (absent any random assignment protocol) accepted it (Saveanu et al. 1994), suggesting that the acceptance rates seen in the study reported here were driven by the acceptability of clozapine rather than other aspects of the study protocol.

Of the 1,300 patients in residence on a particular day, 803 had a qualifying diagnosis (table 1); hence, 298 ($803 \times 0.67 \times 0.63$

× 0.88) would be expected to be appropriate for a clozapine trial. This calculation is based on the likelihood of their having had unsatisfactory responses to past adequate drug trials ($p = 0.67$), assenting to take the drug ($p = 0.63$), and being medically cleared ($p = 0.88$). Thus, in State hospitals with similar residents, we estimate that 22.9 ± 2.2 percent of all current patients and 37.1 ± 3.4 percent of those with a diagnosis of schizophrenia or schizoaffective disorder are appropriate for and would accept a clozapine trial.

Assuming that patients in State hospitals in Connecticut are representative of patients in the public sector nationwide, then the data reported here can be used to estimate the cost of giving all eligible U.S. State hospital residents access to a 1-year clozapine trial. (Data from other States would engender more confidence in such estimates, but the Connecticut data are nonetheless useful for estimating gauging the general magnitude of startup costs.) From Manderscheid and Sonnenschein (1992) one can estimate that approximately 58,246 individuals are receiving care in State and county psychiatric hospitals on any given day. Extrapolating from the Connecticut data, an estimated $39,025 \pm 1,922$ patients hospitalized in public facilities on any given day would meet FDA criteria for clozapine use, and an estimated $21,609 \pm 1,980$ of these inpatients would agree to treatment and be cleared medically. We use the following data from Connecticut to compute the first year's cost of offering clozapine to all eligible long-stay public patients in residence on a given day: a 9 percent discontinuation rate after 2 months due to side effects and pa-

tient preference, growing to a 24 percent discontinuation rate by 12 months; an average price per patient per month of \$625 for clozapine and related blood monitoring; and a reduction in treatment cost of \$10.50 per patient per month due to discontinuation of standard neuroleptics (based on an average of what the State pays for 1,000 mg of chlorpromazine and for an equivalent amount of haloperidol). These calculations yield an estimated cost of \$6,342 for clozapine for 1 patient for 1 year, which translates to a cost of \$137 million (\pm \$12.6 million) to offer up to 1 year of clozapine treatment to all eligible public-sector inpatients hospitalized on a single arbitrary day.

In 1988, national public-sector psychiatric inpatient expenditures were \$7.7 billion annually (Manderscheid and Sonnenschein 1992). Based on this figure, offering all eligible inpatients in the United States a 1-year clozapine trial would require a 1.8 percent increase in public expenditures. Given clozapine's effectiveness in cutting readmission rates, this startup cost could be recouped quickly, depending on the durations of rehospitalizations and on long-term readmission rates. The above estimate represents the difference in cost between hospital bed days for clozapine and those for standard neuroleptics. Not considered are cost differences due to changes in seclusion/restraint, auxiliary services, and workload required for clozapine. Future reports will focus on more detailed analyses of these cost findings.

The estimate of the percentage of patients eligible for a clozapine trial does account for new admissions after the "snapshot" date. It

is therefore weighted toward long-stay State hospital patients and would shift if most of these patients were given a clozapine trial. Depending on assumptions about clozapine eligibility among newly admitted patients, the number of patients appropriate for a trial would, at least initially, be much greater.

It is noteworthy that only about half of long-stay patients with schizophrenia could be confirmed to have had two adequate neuroleptic trials. This fact suggests that our interpretation of the FDA criteria for past drug failures may have been too strict, that psychopharmacology within the State hospitals may be dismayingly static, or that some combination of these and other factors is at work. A more liberal interpretation of the FDA criteria (e.g., not requiring two different classes of neuroleptics or setting less stringent dosage or duration parameters) would have led to even higher estimates of the number of people eligible nationally for a clozapine trial. The clozapine eligibility survey identified all CDMHAS inpatients who had not had two adequate trials and started an ongoing review of pharmacotherapy practices and a series of interventions to improve care (e.g., consultation).

Some findings suggest that failure of two adequate neuroleptic trials may be too stringent a criterion for clozapine eligibility. For example, Lieberman et al. (1993) studied 70 first-episode patients with schizophrenia or schizoaffective disorder and found that 74 percent of those who failed a careful first trial on fluphenazine were still refractory after a subsequent trial on haloperidol. Hence, one could argue that individuals

should be eligible for clozapine after only one failed trial. Our findings suggest that using one failed trial as the criterion would increase the percentage of State hospital residents eligible by record review and diagnosis from 60 to 85 percent.

Perhaps the most surprising findings are the preliminary discharge and readmission figures from the randomized trial; that is, the similar 1-year discharge percentages and the dramatic differences in readmission rates for clozapine and usual care. Yet, the published and unpublished reports from other investigators reviewed at the beginning of this article are consistent with our findings. Discharge rates reported for State hospital patients 1 year after starting clozapine are only slightly higher than the 27 percent rate we found. Reid et al. (1994) found no reduction in bed use from baseline during the first 9 months on clozapine, although the specific 1-year discharge rate was not reported. The subsequent reductions in bed use they observed could have been partly or entirely produced by reduced readmission rates. Wilson and Claussen (1994) reported a 38 percent 1-year discharge rate, and Dennis et al. (1993) reported a 40 percent rate. As for readmission rates, Wilson and Claussen found a 13 percent 6-month readmission rate among 38 discharged clozapine patients, while Dennis et al. found less than a 4 percent return rate among 71 discharged patients. These comparisons do not suggest that any special circumstances in our randomized trial produced this finding of reduced readmission rates associated with clozapine use. They do, however, underscore the

usefulness of a control group in interpreting the extent to which findings are due to clozapine versus regression to the mean on treatment patterns or to trends in the service system under study.

Cost-effectiveness studies such as the one under way in Connecticut will determine whether the cost offsets made possible by clozapine (e.g., reduced readmission rates) make it economically advantageous. Generalizing from the Connecticut experience, State governments will have to invest approximately \$140 million nationwide to give all eligible patients hospitalized on a given day 1 year's access to clozapine. Although improvements in symptomatology, quality of life, and eventual cost savings may occur, States have an uncertain fiscal incentive to prime this putative pump, since much of the potential savings may be realized by payers other than the States, much less by State Departments of Mental Health.

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