

# Cost-effectiveness of Clozapine Compared With Conventional Antipsychotic Medication for Patients in State Hospitals

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**Background:** An open-label, randomized controlled trial compared clozapine with physicians'-choice medications among long-term state hospital inpatients in Connecticut. The goal was to examine clozapine's cost-effectiveness in routine practice for people experiencing lengthy hospitalizations.

**Methods:** Long-stay patients with schizophrenia in a state hospital were randomly assigned to begin open-label clozapine (n=138) or to continue receiving conventional antipsychotic medications (n=89). We interviewed study participants every 4 months for 2 years to assess psychiatric symptoms and functional status, and we collected continuous measures of prescribed medications, service utilization, and other costs. We used both parametric and nonparametric techniques to examine changes in cost and parametric analyses to examine changes in effectiveness. We used bootstrap techniques to estimate incremental cost-effectiveness ratios and create cost-effectiveness acceptability curves.

**Results:** Both groups incurred similar costs during the 2-year study period, with a trend for clozapine to be less costly than usual care in the second study year. Clozapine was more effective than usual care on many but not all measures. With the use of effectiveness measures that favored clozapine (extrapyramidal side effects, disruptiveness), bootstrap techniques indicated that, even when a payer is unwilling to incur any additional cost for gains in effectiveness, the probability that clozapine is more cost-effective than usual care is at least 0.80. These findings were not as evident when outcomes where clozapine was not clearly superior (psychotic symptoms, weight gain) were examined.

**Conclusion:** Clozapine demonstrated cost-effectiveness on some but not all measures of effectiveness when the alternative was a range of conventional antipsychotic medications.

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**C**LOZAPINE has proved to be effective in treating patients with refractory schizophrenia.<sup>1-5</sup> The purpose of this study was to determine, in a randomized trial, the cost-effectiveness of clozapine compared with conventional medication alternatives ("usual care") typically used for patients with treatment-refractory schizophrenia in state hospitals.

Two reviews examining the cost-effectiveness of clozapine have highlighted the preponderance of nonexperimental studies and the need for more rigorous cost-effectiveness studies.<sup>6,7</sup> Three nonexperimental studies comparing the number of hospital days before with the number of hospital days after clozapine treatment concluded that the need for fewer hospital days during clozapine treatment produced cost savings.<sup>8-10</sup> Hospital cost savings associated with clozapine were also reported in studies comparing pa-

tients taking clozapine with those taking conventional medications.<sup>11-15</sup> Similarly, 2 studies comparing patients who continued taking clozapine with those who stopped taking clozapine concluded that patients who continued taking clozapine incurred lower cost.<sup>16,17</sup> However, in a study including more comprehensive costs (inpatient treatment, outpatient treatment, medication, and laboratory test costs), the cost of patient care increased 10% during clozapine treatment compared with costs before clozapine.<sup>18</sup> Limitations of these studies have been noted elsewhere.<sup>6,7,19-24</sup> Nevertheless, evidence typically favors the cost-effectiveness of clozapine over conventional antipsychotic medications.

One other study, a double-blind comparison of clozapine with haloperidol, has reported on clozapine's cost-effectiveness by means of a randomized trial.<sup>5</sup> In that study, hospitalized patients assigned to clozapine did not show statistically

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## SUBJECTS AND METHODS

### SUBJECTS

From November 5, 1991, through August 24, 1992, we approached patients in each of the 3 state hospitals operated by the state mental health agency (then the Connecticut Department of Mental Health [DMH]) who had (1) a chart diagnosis of schizophrenia or schizoaffective disorder; (2) demonstrated a failure to respond to adequate trials (defined as at least 6 weeks at a dosage equivalent to 1000 mg of chlorpromazine per day or resulting in adverse effects such as tardive dyskinesia or neuroleptic malignant syndrome) of at least 2 different antipsychotic medications; (3) a hospitalization of at least 4 months; (4) total hospitalization time of at least 2 of the 5 preceding years; and (5) no medical contraindication to clozapine.<sup>3</sup> Of the 227 eligible patients who completed the informed consent process and agreed to participate, 138 were randomly assigned to begin taking clozapine and 89 were randomly assigned to continue receiving conventional antipsychotic medications, by means of a biased-coin randomization strategy (used to speed the rate at which people had access to clozapine).<sup>2</sup>

### PROCEDURE

Patients assigned to usual care could receive any combination of conventional medications available. Clozapine was the only new antipsychotic medication available (risperidone became available at the end of the study; 3 study participants had risperidone for 24, 35, and 79 days). Treating psychiatrists (state hospital employees with board certification) could prescribe conventional or ancillary medications in addition to clozapine and could discontinue clozapine as they saw fit.

### MEASURES

#### Interviews

Master's level clinicians on the research staff (nurses, clinical psychology graduate students who had completed all requirements except their dissertation) interviewed study participants at study entry and every 4 months thereafter for 2 years. Psychiatric symptomatology was measured by means of the Brief Psychiatric Rating Scale (BPRS).<sup>25</sup> Quality of life was assessed by means of the Quality of Life Inventory.<sup>26,27</sup> The prescribing psychiatrist rated involuntary movement with the Abnormal Involuntary Movement Scale.<sup>28,29</sup> Chart reviews provided demographic data, daily medications, ancillary treatments, monthly side effect ratings, number of hours in special observation (eg, seclusion and restraint), and occurrence of problematic behavior (eg, disruptiveness and assaultiveness).<sup>2</sup>

#### Cost Measures

We derived cost estimates from state fiscal year 1993. We developed estimates of the cost of each type of service by reviewing fiscal records such as the Medicare Cost Report for hospitals and audited expenditure reports for other state-funded agencies. We adjusted specific items when the

expenditure did not reflect true opportunity cost. A cost range representing local market value of rent replaced depreciation value of space, and costs of staff members shared between programs were reallocated proportionately.

For discharged patients, chart reviews and weekly case manager documentation provided information on nights spent in nursing homes, hospitals, shelters, jails, respite units, with friends or relatives because of a crisis, with no place to stay, or some other place because of an emergency. Information regarding state-funded services (inpatient, outpatient, and social rehabilitative services) was obtained from the mental health management information system and monthly reports by service providers. Medicaid records for the period of 2 years after enrollment also provided information on use of nursing homes, private hospitals, emergency departments, and outpatient services. Tracking service utilization and residence from multiple sources enhanced accuracy through confirmation and reconciliation. For example, where there was disagreement on discharge dates between state management information system and case manager report, the patient's chart was examined to determine correct dates (166 nonmatches from 23608 comparisons).

We created high- and low-cost estimates for state hospital days, outpatient services, and ancillary medications. The high-cost estimate for each perspective included the high estimate for the cost of state hospital days, outpatient services, and ancillary medications; the low-cost estimate included the low estimates for these components. To estimate high and low values for inpatient space cost, the range of estimated fair-market values was used. Usual daily dosage range for each ancillary medication and typical charge to Medicaid and the state were compiled. We calculated high- and low-cost estimates by using the high and low end of the ranges of typical daily dosage. The contract clinical laboratory provided Medicaid and state costs for laboratory tests. When an inpatient spent hours in direct observation (suicidal precaution, high assaultiveness risk, seclusion, or restraint), labor costs were increased by 50%, on the basis of costs of restraint in nursing homes.<sup>30</sup>

Self-reported income and benefits allowed estimates of administrative cost of transfer payments and earned income (to measure productivity, treated as a negative social cost). We summed supplemental security income, supplemental security disability insurance, social security retirement or survivors benefits, other social welfare, food stamps, and veterans' benefits, and estimated the administrative cost of these benefits at 8%, the rate for supplemental security income payments.<sup>31</sup>

We examined cost from 3 perspectives: societal, the state of Connecticut, and DMH. Cost to DMH included cost of treatment by agencies operated by DMH, outpatient and residential care funded by DMH, and medications and laboratory tests while in DMH hospitals. The cost to society included all DMH costs plus all other resources used, such as services provided by nonstate hospitals and nursing homes, jail costs, and administrative cost of transfer payments.<sup>32</sup> We subtracted productivity (earned income), as measured by self-report, from the cost to society but not from state or DMH costs. State costs were similar to societal costs, except that only the state 50% share of Medicaid payments was included for general hospitals, emergency department visits, and nursing homes. We also

included in state costs the state supplement to supplemental security income and administrative costs of state-funded transfer payments. The costs of outpatient services, medications, and laboratory tests were 100% when funded by DMH and 50% when covered by Medicaid.

## STATISTICAL ANALYSIS

All analyses used a .05  $\alpha$  level and 2-tailed tests. Two patients were excluded from the cost analyses (they were randomized to clozapine but never began taking clozapine). Only 2 study participants were unavailable for follow-up (both in usual care) and were left as missing for year 2 after their loss for measures of cost and effectiveness. Costs for the 6 patients who died (3 in each condition) were set to 0 after their death so that their costs before death would be retained in the analysis. Measures of effectiveness for patients who died were left as missing after their death.

To determine whether cost perspective (society, state, DMH) or high- vs low-cost estimates would influence findings, we conducted intent-to-treat sensitivity analyses comparing total costs during the 2-year period. We also examined the societal and state costs both with and without their transfer payment components. None of these 10 scenarios produced meaningfully different results. Therefore, all analyses reported herein use the low (conservative) estimate of societal costs that includes transfer payment administrative cost.

We conducted *t* tests to measure group differences on demographic and effectiveness measures at baseline. The details of the analysis methods and effectiveness findings have been reported elsewhere.<sup>3</sup>

As expected, cost distributions were positively skewed (few individuals had extremely high costs), so we conducted *t* tests on transformed scores and applied bootstrapping (resampling) methods to construct confidence intervals (CIs). Bootstrap techniques use every patient's individual data to create an empirical sampling distribution of the test statistic for this population. Bootstrap techniques provide less biased estimates of CIs in highly skewed cost data.<sup>33-35</sup> We also used resampling methods to construct confidence bounds on incremental cost-effectiveness ratios (ICERs).

We conducted analyses with the use of intent-to-treat groupings and under 2 definitions of treatment crossovers. "Treatment-condition crossovers" are patients who, after the study began, switched to the treatment associated with the other arm of the study (eg, the 58 patients assigned to usual care who began a trial with clozapine treatment and the 46 patients taking clozapine who discontinued it). "Medication crossovers" include the treatment-condition crossovers plus the 12 additional patients assigned to usual care who began a trial with a conventional antipsychotic medication other than the one they were taking at randomization.

We consider CIs on cost and ICER estimates as essential for meaningful interpretation of our findings. Although a common practice until recently in economics has been to interpret nonsignificant differences in cost as evidence of cost equivalence, we believe this practice can be misleading. We computed ICERs with the use of total 2-year cost and 4 different effectiveness measures: months free of EPS (rated from patient chart notes in conjunction with Abnormal Involuntary Movement Scale ratings); months with no or minimally disruptive behavior; change in total

BPRS score from baseline to month 24 (scaled 0-6); and percentage weight gained. We selected these effectiveness measures because of their dissimilarity and because they were less confounded with cost than was days hospitalized. Because the relative importance one would assign to these different measures of effectiveness is highly individual and may differ across patients, providers, and payers, we chose not to create a composite effectiveness measure such as a quality-adjusted life-year.

The ICERs were calculated by dividing the difference in cost (clozapine – usual care) by the difference in effectiveness. We used 10000 bootstrap replications to calculate the numerator and denominator of the ICER.<sup>36</sup> Each of the 10000 bootstrap replications was plotted as a point on the cost-effectiveness plane.<sup>37</sup> For each estimate, the difference in effectiveness (clozapine – usual care) is plotted on the x-axis and the corresponding difference in cost (clozapine – usual care) is plotted on the y-axis. This cluster of points displays the sampling distribution of the ICER. The lower right quadrant contains ICERs where clozapine is less costly and more effective than usual care. The upper right quadrant contains estimates where clozapine is more costly and more effective.

Clozapine would clearly be the dominant treatment if it were both less costly and more effective than usual care, yet a payer may be willing to increase spending to improve the probability that the use of clozapine results in at least a given increase in effectiveness. To address this, one can construct vectors on the cost-effectiveness plane that correspond to different ceiling ratios for a payer's willingness to pay. For example, if a payer is unwilling to spend anything, the vector of the ceiling ratio would follow the equation  $y=0x$  (ie, for any increase in effectiveness, there is no additional cost). If a payer is willing to spend \$1000 per each EPS-free month during a 2-year period, the vector of the ceiling ratio would follow the equation  $y=1000x$  and would run through the points (0, 0), (1000, 1), (2000, 2), and so on. In this case, the probability that clozapine is more cost-effective than usual care is represented by the percentage of bootstrap replications falling below the constructed vector (which includes all of the points in the lower right, or "dominant," quadrant plus the points in the upper right quadrant that fall below the vector).

The value of the ceiling ratios corresponding to what a payer is willing to pay will differ across payers. The information from the cost-effectiveness plane can be used to create a cost-effectiveness acceptability curve.<sup>36</sup> The x-axis of the cost-acceptability curve represents the value of the ceiling ratios, which is equal to the constants used to calculate vectors corresponding to the ceiling ratios in the cost-effectiveness plane (eg, the vector corresponding to the equation  $y=1000x$  would be depicted as "1000" on the x-axis of the cost-acceptability curve). The y-axis represents the cumulative probability that clozapine is cost-effective and is calculated as the percentage of bootstrap replications that fall below the vector that corresponds to each value of the ceiling ratio on the x-axis. Given what a payer considers an appropriate incremental expenditure to achieve a given increment in effectiveness of one intervention compared with another (ie, the cutoff for cost-effectiveness for that payer), the cost-effectiveness acceptability curve shows the likelihood that the intervention will, on average, reach that threshold.

**Table 1. Demographic Characteristics and Effectiveness Results\***

	Clozapine (n = 138)	Usual Care (n = 89)	Tests of Significance
Age, mean ± SD, y	42 ± 12	40 ± 11	$t_{225} = 1.83, P = .07$
Sex, No. (%)			
M	84 (61)	54 (61)	$\chi^2_1 = 0.00009, P = .98$
F	54 (39)	35 (39)	
Marital status, No. (%)			
Never married	112 (81)	77 (87)	$\chi^2_2 = 1.13, P = .57$
Currently married	7 (5)	3 (3)	
Widowed, divorced, or separated	19 (14)	9 (10)	
Educational level, No. (%)			
<7 y of school	16 (11)	10 (11)	$\chi^2_4 = 3.24, P = .52$
Junior high school	63 (46)	37 (42)	
Completed high school	51 (37)	38 (43)	
Received 4-y college degree	3 (2)	0 (0)	
Completed postgraduate training	1 (1)	0 (0)	
No information available	4 (3)	4 (4)	
Age at first hospitalization, mean ± SD, y	20 ± 5	19 ± 4	$t_{220} = 1.84, P = .07$
Age at first psychotic symptom, mean ± SD, y	18 ± 6	17 ± 5	$t_{211} = 1.85, P = .07$
Current admission length of stay, mean ± SD, y	8.5 ± 8.2	8.2 ± 7.7	$t_{225} = 0.26, P = .80$
Baseline antipsychotic medication, No. (%)†‡			
1 Antipsychotic medication	127 (93)	84 (94)	$\chi^2_2 = 0.67, P = .72$
2 Antipsychotic medications	8 (6)	5 (6)	
None	1 (1)	0 (0)	
EPS-free months during 2 y‡	18	14	$t_{146} = 3.4, P = .001$
Disruptiveness-free months during 2 y‡	10	6	$t_{198} = 3.9, P < .001$
Weight gain during 2 y, %‡	7	5	$t_{98} = 0.7, P = .51$
Change in total BPRS during 2 y‡	1	3	$t_{213} = -1.3, P = .20$

\*EPS indicates extrapyramidal symptom; BPRS, Brief Psychiatric Rating Scale.

†The most common single antipsychotic medications prescribed at baseline in the clozapine and usual care groups, respectively, were haloperidol (20.5% and 31%), chlorpromazine hydrochloride (20.5% and 17.9%), and fluphenazine hydrochloride (16.5% and 17.9%).

‡N = 136. Removed 2 subjects assigned to clozapine who never began taking clozapine.

significant cost savings. However, patients assigned to clozapine experienced significantly fewer hospital days, psychiatric symptoms, and extrapyramidal side effects (EPSs).<sup>5</sup> Because clozapine was more effective and was not significantly more costly, it may be more cost-effective than haloperidol among heavy users of inpatient services.

It would be valuable to know not only that clozapine is cost-effective compared with haloperidol, but whether it also surpasses other medication regimens selected and adjusted by prescribing physicians. To address this question, the Connecticut Department of Mental Health and Addiction Services, Hartford, conducted an open-label, randomized, controlled trial of clozapine against physicians'-choice medications among long-term state hospital inpatients.

## RESULTS

### EFFECTIVENESS

**Table 1** expands on demographic and treatment characteristics of the sample and effectiveness results that have been reported previously.<sup>2</sup> Treatment groups did not differ in their rate of discharge from the hospital, but, once discharged, the clozapine group was less likely to be re-admitted. Patients treated with clozapine also became significantly less disruptive and required significantly fewer as-needed antipsychotic medications than did patients in the usual care group. Clozapine-treated patients ex-

perienced significantly fewer EPSs. The groups did not differ with respect to weight gain or change in total BPRS score. This pattern of results did not change when treatment crossovers were excluded.<sup>2,3</sup>

### COST

**Figure 1** shows the pattern of average societal cost by category for patients assigned to clozapine and to usual care for years 1 and 2 (costs from state and DMH perspectives were very similar and are available from the authors).

Patients assigned to clozapine accrued, on average, \$1112 more cost in year 1 but \$7149 less cost in year 2 than did patients assigned to usual care (**Table 2**). These means did not differ significantly for year 1, year 2, or total costs during the 2-year period, whether raw or transformed scores were used. The 95% CI estimated by bootstrap methods included zero between-group differences in cost for both intent-to-treat analyses (95% CI, -\$22 594 to +\$9509) and when treatment crossovers were excluded (95% CI, -\$38 073 to +\$15 380).

### COST-EFFECTIVENESS

Given that clozapine was more effective than usual care on some but not all effectiveness measures but fairly similar to usual care on cost, we computed ICERs for distinct effectiveness measures to detail more thoroughly the policy implications. We estimated ICERs for 4 effec-

tiveness measures: EPS-free months, disruptiveness, psychiatric symptomatology, and weight gain. The ICERs for number of EPS-free months indicated that there is a 0.80 probability that clozapine is cost-effective (**Figure 2**) (note that about 80% of the ICER estimates fall in the lower right quadrant). However, the upper limit of the 95% CI for the intent-to-treat and the crossovers-excluded analyses falls in the upper right quadrant of Figure 2, indicating that there is a nontrivial likelihood that clozapine will be both more costly and more effective than usual care. The exclusion of crossovers (under either of the definitions given) increased the apparent effectiveness of clozapine (the crossovers-excluded oval is shifted to the right of the intent-to-treat oval), increased the variability of the cost and effectiveness estimates (the crossovers-excluded oval is larger), and decreased the estimate of the relative costliness of clozapine (the crossovers-excluded oval is shifted lower by about \$5500) (Figure 2). The ICERs for disruptiveness, another effectiveness measure favoring clozapine, produced results similar to those for EPS (again, about 80% of the ICER estimates fell within the lower right quadrant of the cost-effectiveness plane).

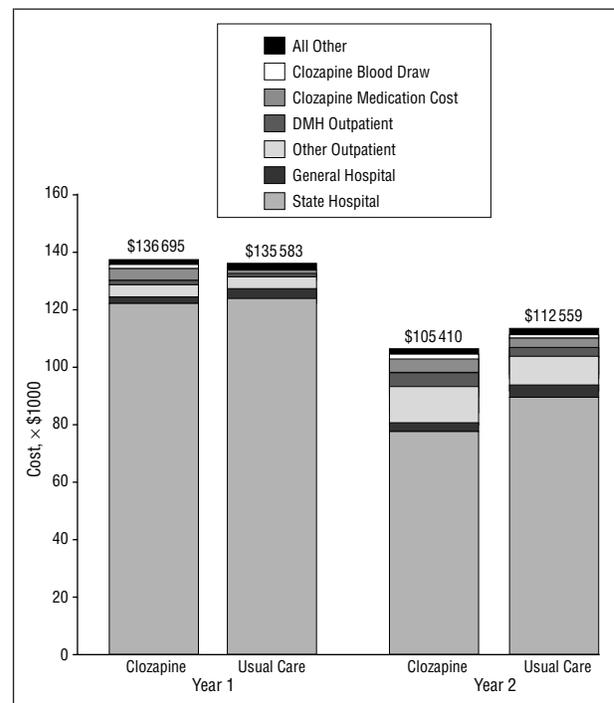
In contrast, ICERs that used effectiveness measures not favoring clozapine produced markedly lower probability estimates of cost-effectiveness, with greater differences between the results of intent-to-treat and crossovers-excluded analyses. For example, in the ICER for change in total BPRS score under intent-to-treat analyses, only 8% of the estimates fell within the lower right quadrant of the cost-effectiveness plane (where clozapine was both more effective and cost less than usual care), while 72% fell within the lower left quadrant, indicating that clozapine will be less expensive but also less effective than usual care for this outcome. When crossovers were excluded, the corresponding increase in effectiveness shifted more of the estimates to the lower right quadrant (68% of the estimates fell within this quadrant). In contrast, the opposite shift occurred for ICERs for weight gain: 32% of the observations fell within the lower right quadrant under intent-to-treat analyses, while only 11% of the estimates fell within this quadrant when crossovers were excluded.

The increments in the likelihood that clozapine is cost-effective given increments in the amount a payer is willing to pay for such effectiveness were examined by plotting cost-effectiveness acceptability curves using reduction in EPS as the effectiveness measure (**Figure 3**). As noted above and illustrated in Figure 2, if the payer is not willing to incur any additional cost, there is still about a 0.80 probability that using clozapine will be cost-effective. If

the payer is willing to incur \$500 in additional cost per year, the probability that using clozapine rather than usual care will achieve greater gains in effectiveness within the ceiling budget increases to 0.90 (Figure 3). The payer who is willing to incur \$1000 in additional cost per year can be virtually certain that using clozapine rather than usual care will achieve greater gains in effectiveness within that payer's ceiling budget (Figure 3).

**COMMENT**

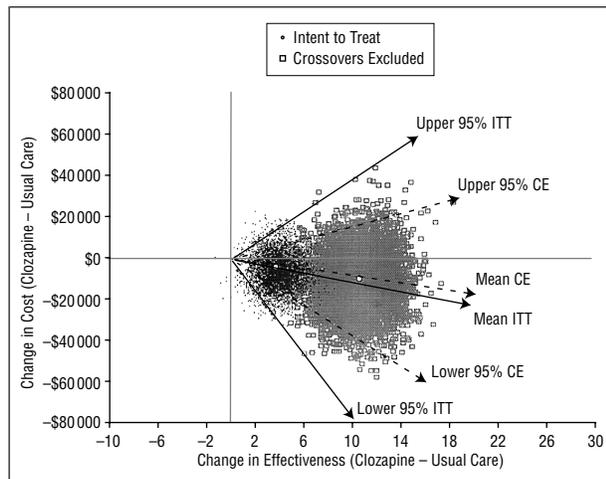
We conclude that clozapine demonstrated cost-effectiveness for some but not all measures of effectiveness among long-stay patients in state hospitals when the alternative was a range of conventional antipsychotic medications. On balance, the confidence surface gives us good reason to think that the true value of the relative cost is not greater for clozapine in the long run. A few outcome variables show clozapine to be more advanta-



**Figure 1.** Mean costs to society for study participants assigned to clozapine (n=136) and usual care (n=89 in year 1, n=87 in year 2); intent-to-treat groupings. The "all other" category includes, in order of decreasing amount (averaged across both groups and both years), nursing home, conventional antipsychotic medications, administration of transfer payments, laboratory tests, ancillary medications, emergency department visits, and jail. DMH indicates Department of Mental Health.

**Table 2. Descriptive Statistics and Confidence Intervals for Total Societal Costs**

	Clozapine				Usual Care			
	No. of Subjects	Mean (SE), \$	25th Percentile, Median, and 75th Percentile, \$	Bootstrap 95% Confidence Interval, \$	No. of Subjects	Mean SE, \$	25th Percentile, Median, and 75th Percentile, \$	Bootstrap 95% Confidence Interval
Year 1	136	136 695 (1916)	131 290, 143 866, 147 655	132 740-140 279	89	135 583 (2352)	133 164, 140 613, 144 085	130 902-140 103
Year 2	136	105 410 (4082)	62 070, 119 993, 145 587	96 847-114 308	87	112 559 (4738)	78 064, 134 806, 143 046	103 665-121 144
Total	136	242 106 (5438)	197 512, 263 019, 292 221	231 085-253 136	87	248 735 (6068)	222 045, 273 894, 283 820	236 417-260 020



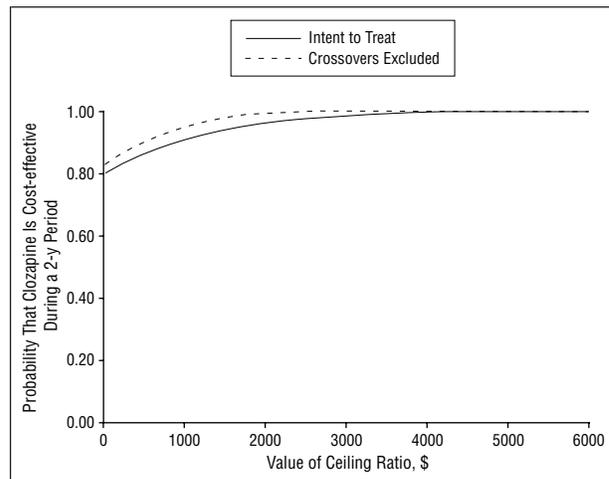
**Figure 2.** Ten thousand bootstrap replications plotted in the cost-effectiveness plane (intent to treat [ITT],  $n=136$  for clozapine and  $n=87$  for usual care; treatment crossovers excluded [CE],  $n=89$  for clozapine and  $n=30$  for usual care). The x-axis and y-axis, respectively, show the difference between clozapine and usual care groups in estimated number of months free of extrapyramidal symptoms and total cost during a 2-year period. The quadrant to the lower right of the origin (0, 0) contains those estimates where clozapine was found to be less costly and more effective than usual care (80% of the estimates for the intent-to-treat analyses and 81% of the estimates when treatment crossovers are excluded).

geous, while most did not demonstrate a significant difference. Thus, any preference-weighting scheme would show the net effectiveness of clozapine to be slightly higher than that of usual care (as a point estimate) and is very unlikely to show a CI that does not include zero difference and some possibility of a negative difference in effectiveness.

One important finding was that clozapine substantially reduces the risk of rehospitalization for those who are discharged. We did not construct a cost-effectiveness surface with the use of reduction in inpatient days or increase in community tenure as the effectiveness measure because such measures are confounded with cost, and it is misleading to have cost-related variables in both the numerator and the denominator of an incremental cost-effectiveness ratio. Nevertheless, most patients, clinicians, and other stakeholders would prefer less hospitalization to more, as a quality-of-life issue, and not just as a way to reduce cost. From this viewpoint, our presentation of findings may somewhat understate the relative advantage of clozapine over conventional antipsychotics.

The comparison of clozapine with usual care may be more conservative than comparing clozapine with a single conventional antipsychotic medication, such as in the Veterans Affairs (VA) study comparing clozapine with haloperidol.<sup>23</sup> In the present study, the conventional medications were chosen by prescribing psychiatrists to suit patients as optimally as possible. Furthermore, in contrast to many randomized trials where patients in each treatment condition are required to change to a new medication, patients assigned to usual care were not required to change to a new medication; hence they avoided the risks of such transitions.<sup>38</sup>

These data are useful to payers and policymakers who wish to estimate the impact of offering clozapine to pa-



**Figure 3.** Cost-effectiveness acceptability curves showing the cumulative probability that clozapine will be cost-effective (ie, that clozapine will achieve greater gains in effectiveness within the a payer's ceiling budget than will usual care; intent to treat,  $n=136$  for clozapine,  $n=87$  for usual care; treatment crossovers excluded,  $n=89$  for clozapine,  $n=30$  for usual care). The x-axis represents values of ceiling ratios (the amount the payer is willing to pay over and above the cost of usual care), and the y-axis represents the cumulative probability that clozapine is cost-effective (the percentage of bootstrap replications that fall below a vector that corresponds to each value of the ceiling ratio on the x-axis corresponds to the probability that using clozapine rather than usual care will achieve greater gains in effectiveness within the ceiling budget).

tients with treatment-refractory schizophrenia. However, the enormous CIs for the cost estimates underscore the large variability in costs across patients in each treatment condition and the resultant susceptibility of the data to varying interpretations depending on the statistical analyses and groupings used. Because the bulk of the range spanned by the cost CIs includes the values where clozapine costs less than or the same as usual care, economists would call clozapine the dominant alternative. However, the broad distribution of possible outcomes underscores the importance of going on to create estimates of cost-effectiveness and describing their variability. We serve both patients and policymakers best by presenting the range of possible outcomes and their relative likelihood.

Like the present study, the VA study found that clozapine decreased hospital days and EPSs but failed to demonstrate a cost savings for one treatment condition over the other by means of intent-to-treat analyses. In both studies there was a trend for the clozapine group to cost less.<sup>5</sup> Whereas the VA study found improvement in psychiatric symptoms, the present study did not.

There are considerable differences between the VA study and the present study, in terms of research design, patient population, and the construction of groups for the crossovers-excluded analyses. Only 11 patients (4.8% of the sample) from the present study would have met the VA study's inclusion criterion of a current hospitalization of 1 year or less. The present study followed up patients for 2 years of open-label treatment. In contrast, the VA study was a 1-year, double-blind comparison in which all study participants underwent weekly blood draws as long as they continued to take the medication they were assigned to at study entry (clozapine or

haloperidol). In the VA study, the blood draw in the control condition may have lessened patients' willingness to continue their current treatment (in that they were tolerating a weekly blood draw without receiving the gains in effectiveness associated with clozapine), which would have diminished the effectiveness estimates from intent-to-treat analyses because of the greater dropout in the haloperidol condition.

The VA study and the present study each have the interpretive strengths associated with effectiveness studies carried out in routine practice settings. However, they are susceptible to the error introduced when individuals stop receiving the treatment to which they were randomly assigned. In the present study, such deviations were minimal for the first 9 months of the study because of the rationing of clozapine during that time.<sup>2-3</sup> The importance of intent-to-treat analyses, and the unspecified biases of crossovers-excluded analyses, are well documented.<sup>39</sup> Nevertheless, when crossovers are common, investigators present analyses that exclude crossovers as proxies for the best-case scenarios for each treatment condition, thereby introducing biases such as those illustrated in Figure 2. Such analyses compare only those who do well enough with treatment A to continue using it with only those who do well enough with treatment B to continue using it.

In the present study, because a variety of medications were represented in the usual-care condition, we created the crossovers-excluded groups in 2 ways. Under one definition (treatment-condition crossovers excluded), individuals were included in the analyses as long as they received treatment with the medications allowed in the treatment condition to which they were assigned (clozapine vs other antipsychotics). Under the narrower definition (medication-crossovers excluded), individuals were included in the analyses only if they continued to be prescribed the medication they were taking at the onset of the study (clozapine vs the conventional antipsychotic taken at study entry). These 2 definitions resulted in very similar results in the present study, likely because, in the present study, most patients (79% [46/58]) assigned to usual care who switched medications changed to clozapine, and hence were excluded under either of the definitions of crossovers. This was not the case in the VA study, where a minority (31% [49/157]) of the individuals in the haloperidol condition who switched medications changed to clozapine.

For the haloperidol control group in the VA study, only individuals who discontinued haloperidol and began clozapine were excluded in the crossovers-excluded analyses (ie, these were "treatment-crossovers excluded" analyses). Hence, by the end of the VA study, even in the crossovers-excluded analyses, the control condition included mostly individuals who were taking open-label medication other than haloperidol, usually another conventional antipsychotic. This inclusion of so many individuals who had done poorly enough with haloperidol that they changed medications, but who were not given a trial of clozapine, may have artificially increased the difference in effectiveness between groups because the crossovers-excluded comparison was largely one of

responders to clozapine vs nonresponders to haloperidol. This may explain why, when crossovers were excluded, group differences in quality of life emerged for the VA study but not for the present study.

Most dramatically in the present study, clozapine was effective in preventing rehospitalizations among patients who had experienced lengthy, recent hospital stays. Individuals taking clozapine were less disruptive and had fewer stigmatizing body movements than those who received usual care, and these differences may have contributed to their increased community tenure. From the perspective of total societal cost, this decrease in hospital use resulted in sufficient cost savings to pay for the increased costs associated with the medication and increased use of outpatient services. In contrast to this overall picture of cost-effectiveness, clozapine would look more or less costly from the perspective of different payers. For example, from the perspective of a capitated payer at risk for pharmacy or outpatient costs but not inpatient care, clozapine would be viewed as an intervention that increased costs. Had the study population included individuals who were hospitalized less often,<sup>40,41</sup> or individuals taking the atypical antipsychotic medications introduced after clozapine, these cost savings may not have materialized. Cost-effectiveness comparisons among the new agents are very important and need to be done with sufficiently long-term follow-up and with careful attention to the cost features illustrated in the present study.

Whatever the study population or medications under study, from a public health perspective, the absence of cost savings should not spell doom for an intervention. Expecting an intervention to pay for itself or at least be cost-neutral before it is disseminated widely is a very high standard rarely adopted in medical care. With clozapine, as with other expensive interventions, payers and policymakers need information on what benefits can be expected given a specified investment in an intervention. The cost approach in the present study—deriving cost-effectiveness acceptability curves and presenting data as such continuous functions—allows payers and policymakers to select their own cost cutoffs with respect to the probability that using clozapine rather than usual care will achieve greater gains in effectiveness within a specified ceiling budget.<sup>36</sup>

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