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Should Clozapine Continue to be Restricted to Third-Line Status for Schizophrenia?: A Decision-Analytic Model

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Abstract

Background: Clozapine is currently restricted to patients who have failed at least two trials of other antipsychotic medications because of concerns that its use as a first–line agent would lead to greater mortality, mainly through agranulocytosis.

Aims of the Study: We sought to determine the cost-effectiveness of allowing clozapine to be a first-line treatment versus the current policy of restricting clozapine to third-line status.

Methods: We performed a cost-effectiveness analysis using published data from randomized controlled trials and epidemiologic studies. The target population was patients with schizophrenia in an acute psychotic episode, with a lifetime time horizon and societal perspective. Outcome measures included life expectancy, quality-adjusted life expectancy, costs, and cost-effectiveness ratios.

Results: Using clozapine as a first agent would lead to modest gains in life-expectancy as well as quality-adjusted life expectancy, relative to restricting its use to patients who failed 2 conventional antipsychotics. The cost-effectiveness ratio of using clozapine first vs. using clozapine third would be $24,100 per quality-adjusted life year (QALY). In 1-way and probabilistic sensitivity analyses, these findings were robust to a variety of assumptions.

Discussion: Allowing clozapine to be a first-line agent may lead to small gains in life expectancy at moderate but acceptable costs.

Implications: While these results do not shed light on whether clozapine should be the *preferred* first-line strategy, they do suggest that clozapine should be added to the armamentarium of *possible* treatments for treatment-sensitive as well as treatment-resistant schizophrenia.

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Background

In 1989, the U.S. Food and Drug Administration (FDA) approved clozapine as a treatment for schizophrenia. However, the FDA restricted clozapine to third-line status, only allowing it to be used after a patient has failed at least two different antipsychotic medications for lack of response or intolerable side effects.[1-3] This restriction of clozapine to use in treatment-resistant patients arose out of concern that if clozapine were used as a first-line agent, it would lead to increased mortality. In pre-marketing studies clozapine was found to cause potentially fatal agranulocytosis in approximately 1% of patients.[4,5] Because this risk was reversible if detected early, weekly monitoring of patients' white blood cell counts was required;[5] this further added to the cost associated with clozapine treatment, which already greatly exceeded that of conventional antipsychotic therapy due to higher drug costs.[6] Restricting clozapine to treatment-resistant patients was also supported by the fact that early clinical trials showing greater efficacy for clozapine vs. conventional antipsychotics were conducted mainly in treatment-resistant populations.[7]

However, in the decade since this restriction on clozapine to third-line status was imposed, much additional evidence has emerged concerning its risks and benefits. A recent meta-analysis[8] and other randomized trials[9] conducted among treatment-sensitive as well as treatment-resistant patients have found that clozapine is significantly more likely than

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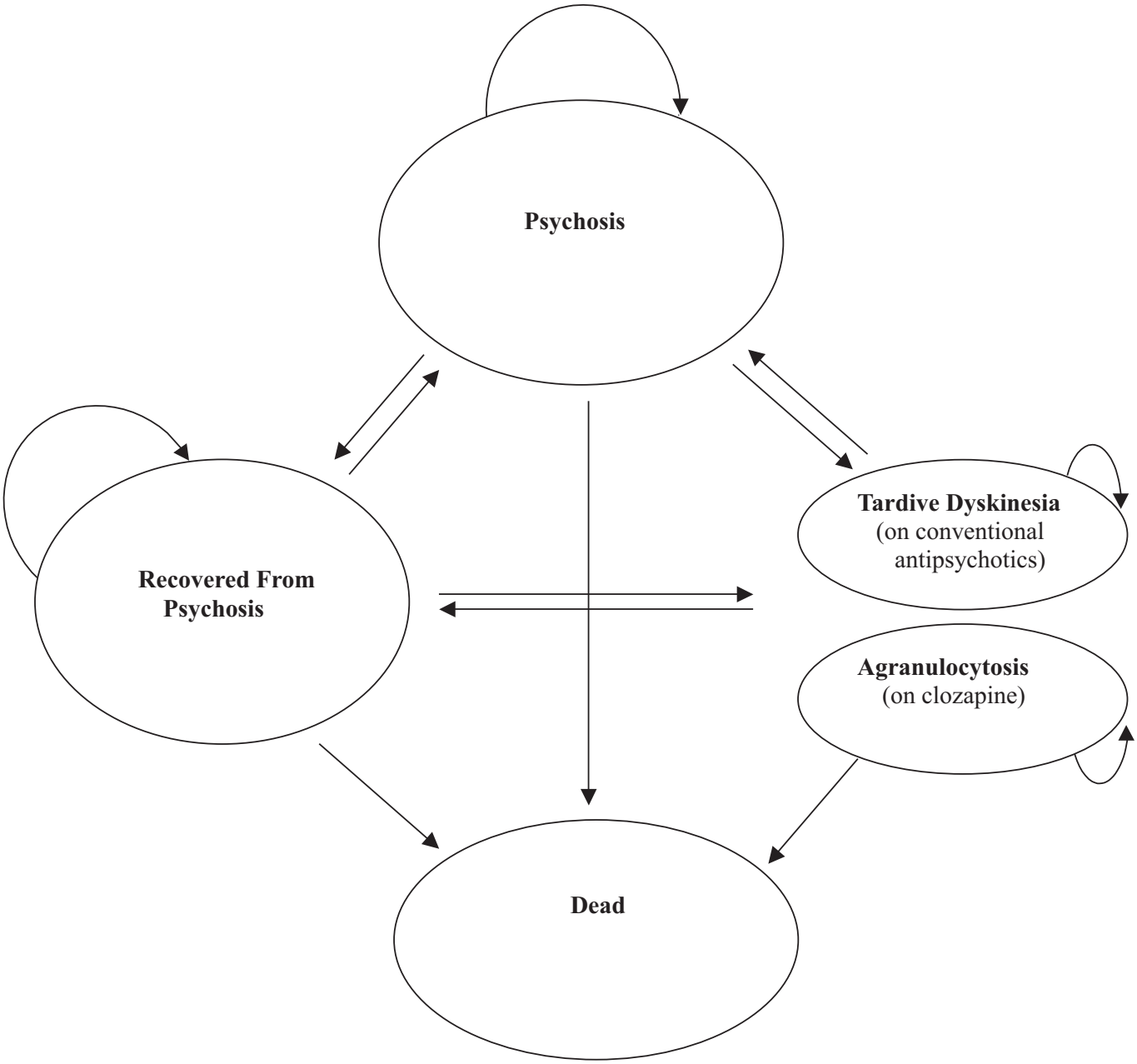

Figure 1. Schematic Diagram of the Markov Model.

Note: **Figure 1** presents a schematic diagram of the Markov model used in this analysis. Health states are in ovals. Arrows represent allowed transitions. At inception all patients start in the psychosis state. From there, patients can remain psychotic, recover from their psychotic episode, go on to have intolerable side effects (i.e., tardive dyskinesia if on a conventional antipsychotic or agranulocytosis if on clozapine), or die.

conventional antipsychotics to improve psychotic episodes and prevent relapse. More recent data from the Clozaril National Registry in the U.S. has also shown that the incidence of agranulocytosis on clozapine, and fatality resulting from it, are substantially lower than originally feared.[10] This has led the FDA to relax its requirement for weekly white blood cell (WBC) monitoring, somewhat reducing the costs associated with clozapine therapy. Clozapine has been shown to be relatively free of the extrapyramidal side effects associated with conventional antipsychotics, and in fact may be a treatment for tardive dyskinesia.[11] Clozapine use has also been associated with lower rates of suicide attempts and completed suicides.[12-15] Generic forms of clozapine have now become available, further lowering its cost.[16]

This evidence suggesting greater benefits and potentially lower risks and costs for clozapine has led to the question of whether the indications for clozapine should be expanded to include use as a possible first-line agent in treatment-sensitive patients.[14,17] Unfortunately, formal analyses of this question are lacking. Cost-effectiveness analyses performed to date have generally been limited to comparisons of

clozapine vs. conventional antipsychotics among exclusively treatment-resistant populations.[18-29] These have consistently shown clozapine to have favorable cost-effectiveness ratios for treatment-resistant patients.

Our first aim was to assess whether clozapine should be a *possible* first-line treatment for schizophrenia, relative to restricting clozapine for only patients who have failed two trials of other antipsychotics. Using data from randomized controlled trials and epidemiologic studies, we modeled the clinical and economic outcomes of these two strategies in a hypothetical cohort of patients with schizophrenia undergoing an acute psychotic episode. Because clozapine is currently underutilized even among treatment-resistant patients,[30] we also compared strategies using clozapine to the common strategy of never using it.

Finally, it is important to distinguish these aims from a question regarding clozapine that this study was not designed to answer. Newer atypical antipsychotics (e.g., risperidone, olanzapine, and quetiapine) are now widely available and used,[31] raising the question of whether these newer agents or clozapine should be the *preferred* first-line treatment in schizophrenia. Trials completed to date indicate the possibility that clozapine may have greater efficacy.[15,32] However, definitively answering what should be the *preferred* first-line treatment will have to wait until sufficient head-to-head trials comparing clozapine to newer atypical antipsychotics in treatment-sensitive patients, such as the recent InterSePT trial,[15] are completed.

Methods

Data Analytic Procedures

Model

We developed a computer model based on all available data from the clinical literature to estimate the outcomes of three treatment strategies in a hypothetical 30-year old patient with schizophrenia hospitalized with an acute psychotic episode (30 years of age was chosen, rather than younger, to accommodate the later ages of onset in women)[33,34]. The *clozapine-third* strategy described the likely outcomes of using clozapine only after a patient had failed 2 trials of conventional antipsychotics; it consisted of the following:

(i) initiating treatment with a conventional antipsychotic;
(ii) switching to a second conventional antipsychotic if the patient fails to recover to the point of being dischargeable from the hospital, or relapses after recovery, or develops serious tardive dyskinesia (TD) on the first conventional antipsychotic;
(iii) following this, switching to clozapine if the patient fails to recover to the point of being dischargeable from the hospital, or relapses after recovery, or develops serious TD on the second conventional antipsychotic;
(iv) switching back to a conventional antipsychotic if the patient fails to recover to the point of being dischargeable from the hospital, or relapses after recovery, or develops agranulocytosis on clozapine.

By contrast, the *clozapine-first* strategy consisted of the following:

(i) initiating treatment with clozapine;
(ii) switching to and remaining on conventional antipsychotics if the patient fails to recover to the point of being dischargeable from the hospital, or relapses after recovery, or develops agranulocytosis on clozapine.

We also examined a third strategy that consisted of using only conventional antipsychotics (i.e., never using clozapine even in treatment-resistant patients). We employed this *conventional antipsychotic only* strategy in subanalyses to estimate the cost-effectiveness of strategies using clozapine in mental health care systems which do not utilize clozapine and offer only conventional antipsychotics to treatment-resistant patients.

We then developed a Markov model[35] of transitional probabilities in which patients could occupy one of seven types of health states: acute psychosis while taking clozapine, acute psychosis while taking conventional antipsychotic, recovered with clozapine, recovered with conventional antipsychotic, serious TD with conventional antipsychotic, agranulocytosis with clozapine, or dead. We then conducted a cohort simulation to track transitions between states representing the expected clinical and economic effects in patients hypothetically randomized to one of the three antipsychotic strategies (see **Figure 1**). A cycle length of 3 months was used. We adopted the societal perspective in our analysis. The model was constructed using the DATA 3.5 decision analysis program (TreeAge Software; Williamstown, MA).

Transition Probabilities

Each state of the model has a mortality rate associated with it, which in turn determines the probability of death in any given cycle (see **Table 1**). The mortality hazard for each state was calculated by combining the effects of suicide while on a specific antipsychotic regimen, death by agranulocytosis while on clozapine, and age-adjusted all-cause mortality rates from U.S. life tables.[36] To reproduce the life-expectancies observed in published record linkage studies of treated schizophrenia patients,[37] we multiplied age-adjusted all-cause mortality rates in U.S. life tables by a factor of four. We modeled death due to suicide or agranulocytosis as additive effects to age-adjusted mortality. The rate of death by suicide while on conventional antipsychotics was derived from published record-linkage data for treated patients with schizophrenia.[37] The rate of death by suicide while taking clozapine was obtained from registry data on the cumulative incidence of suicide among 51,333 patients.[13] The rate of death from agranulocytosis while taking clozapine was obtained from Clozaril National Registry data from 1990-1994.[10] For sensitivity analyses, we used the upper and lower bounds of the 95% confidence interval around the estimates of the rates of death by suicide and agranulocytosis.

Data on the effectiveness of clozapine vs. conventional antipsychotics in treatment-sensitive and treatment-resistant patients with schizophrenia were obtained from a recent

Table 1. Assumptions Governing Transition Probabilities, Costs, and Utilities for the Markov Model

Variable	Base Case	Biased Toward Clozapine First	Biased Toward Clozapine Third	Literature Reference
3-Month Probabilites on Conventional Antipsychotic				
Psychosis to recovered	40.0%	34.1	46.0	(8)
Recovered to relapse	13.0%	15.5	10.4	(8)
No TD to TD	1.3%	1.7	0.9	(38)
Death by suicide	0.07%	0.08	0.05	(25)
3-Month Probabilities on Clozapine				
Psychosis to recovered	42.9%	48.9	36.8	(8)
Recovered to relapse	8.0%	5.9	10.1	(8)
No agran. to agran.	0.019%	0.017	0.021	(10)
Agranulocytosis to death	3.141%	1.392	4.891	(10)
Death by suicide	0.02%	0.01	0.02	(13)
3-Month Costs				
Medication				
Clozapine (425 mg/d)	$1,207	905	1509	(16)
Haloperidol (15 mg/d)	$9	11	7	(16)
WBC monitoring	$297	223	371	(6)
Inpatient psych. hospital.	$11,512	14,390	8634	(44)
Outpatient care	$1940	1455	2425	(21)
Residential treatment	$2026	1520	2533	(21)
TD treatment	$56	70	42	(46)
Agranulocytosis treatment	$10,982	13,728	8237	(45)
Quality Weights Assigned to Health States				
Recovered from psychosis	0.83	0.62	1.00	(40)
Actively psychotic	0.56	0.42	0.70	(40)
Agranulocytosis	0.46	0.58	0.35	(41)
TD	0.69	0.52	0.87	(25)
Discount Rate (annual)	3%	0	5	(42)

meta-analysis of all data from randomized controlled trials.[8] To estimate the probability of recovery from psychosis under different regimens, we used data on the end point of dischargeability from the hospital at the end of short-term trials. Although clozapine demonstrated greater effectiveness on the endpoint of clinical improvement (based on change in symptom severity rating scores), we used dischargeability from the hospital because it may be a better proxy for clinically meaningful improvement, and is likely to produce a more conservative estimate of the relative effectiveness of clozapine.

The meta-analysis was also the source of data on the short-term effectiveness of clozapine or conventional antipsychotics to prevent relapse of recovered patients.[8] The upper and lower bounds of the 95% confidence interval (C.I.) around each estimate of effectiveness from the meta-analysis were used in sensitivity analyses of the probabilities of recovery and relapse. We conservatively used only the probability of developing the most serious extrapyramidal symptoms such as TD,[38] without considering the probabilities of developing other extrapyramidal symptoms such as Parkinsonism, dystonias, or akathisia.

In estimating the proportion of recovered patients who would relapse within 3 months if their antipsychotic was withdrawn due to side effects, we used a published estimate[39]; its 95% CI was used in sensitivity analyses.

Health Effects

To measure the health effects of strategies, we started by recording the unadjusted life expectancies (i.e., life years) associated with each (see **Table 1**). We then calculated our main measure of the health effects of each strategy in terms of quality-adjusted life years (QALYs). QALYs are calculated by multiplying the life years spent in specific health states by the quality of life weights associated with those states. We used published quality-of-life weights for the health states in schizophrenia, derived from standard gambles, rating scales, and paired comparison questions[40] (see **Table 1** for the actual quality weights assigned to health states). The decrement in quality of life assigned to TD was estimated from standard gambles and rating scales carried out among patients with schizophrenia.[25] Since no quality of life weight for agranulocytosis has been calculated, we employed values assigned to severe infection while immunosuppressed from cancer chemotherapy;[41] to the extent that agranulocytosis is a less serious clinical condition, this biased our results against the clozapine-first strategy. To define a range for sensitivity analyses, we subtracted 25% to estimate a lower bound and added 25% for the upper bound. We also conducted a sensitivity analysis in which health states were not adjusted for such quality-of-life differences.

Costs

In the base case, we included the following direct medical costs for each strategy (see below for sources): hospitalization for psychotic episodes, outpatient care, residential treatment costs, and antipsychotic medication costs (see **Table 1**). To be conservative, we assigned to clozapine users who developed agranulocytosis the expense of hospitalization for this condition. All clozapine users also were assigned a weekly cost for WBC monitoring. Conventional antipsychotic users who developed serious TD experienced the cost of pharmacologic treatment for this side effect. We inflated all costs to 1999 U.S. dollars using the medical care component of the Consumer Price Index (CPI-M).[42]

To calculate drug costs, our base case assumed that clozapine users took 425 milligrams daily while conventional antipsychotic users took 15 mg of haloperidol daily; these dosages were chosen because they correspond to the median of recommended therapeutic dose ranges.[1,2,43] We calculated the costs of the drugs based on the average wholesale price of generic clozapine and generic haloperidol.[16]

Psychiatric hospitalization costs are for a stay of mean length (23 day) and based on the average cost for all stays in inpatient mental health settings in the U.S. as identified by the Inventory of Mental Health Organizations and General Hospital Mental Health Services.[44] Three-month outpatient and residential treatment costs were obtained by first calculating the average number of units of treatments and services used by patients with schizophrenia followed for a 2-year period;[21] average numbers of units were then multiplied by median costs per unit identified from psychiatric records and administrative (Medicaid) data.[23] Hospitalized patients were assigned outpatient and residential treatment costs for the proportion of 3-month cycles during which they were not inpatients.

The 3-month cost of WBC monitoring was based on a published estimate for weekly WBC testing.[6] Weekly WBC testing was assumed rather than the currently recommended monitoring strategy because our estimates of the occurrence and fatality from agranulocytosis derive from a time when weekly WBC testing was required. This assumption also creates a more conservative estimate of the cost of the clozapine-first strategy if agranulocytosis is equally well detected by WBC monitoring every two weeks. The cost of treating agranulocytosis is based on published estimates and includes hospitalization costs.[45]

In an attempt to manage TD, clinicians frequently try pharmacologic treatments which may or may not be successful;[43] a cost for 3 months of pharmacologic treatment (e.g., benztropine) was assigned to those who developed TD as a result of conventional antipsychotic use.[46]

To define a range for the sensitivity analyses of each cost estimate, we subtracted 25% of the cost for the lower bound and added 25% for the upper bound.

Probabilistic Sensitivity Analyses

In addition to conducting sensitivity analyses on individual variables, we used Monte Carlo simulation to vary transition probabilities, costs, and utilities simultaneously.[47] A probability distribution was created for each variable on the basis of the 95% CI or other range used in 1-way sensitivity analyses described above. New values from each probability distribution were randomly selected during each of 1000 iterations, and cost and effectiveness of each strategy were calculated accordingly.

Discounting

We discounted all costs and health effects at an annual rate of 3% for the base case, with sensitivity analyses performed between 0% and 5%.

Results

Base-Case Analysis

For 30-year-old patients with schizophrenia, the undiscounted annual costs under the clozapine-first, the clozapine-third, and the conventional antipsychotics only strategies were $26,650, $26,640, and $26,530, respectively. The undiscounted life expectancies under these three strategies were 31.03, 31.01, and 30.92 years, respectively.

After discounting at 3% annually, the total discounted costs for the clozapine-first, clozapine-third, and conventional antipsychotic only strategies were $514,100, $513,800, and $509,200, respectively (see **Table 2**, column 1). After discounting and quality-adjusting for time spent in each health state, the three strategies yielded 14.59, 14.58, and 14.51 discounted quality-adjusted life years (QALYs)(see **Table 2**, column 2).

Thus under base case assumptions, our main finding is that the hypothetical strategy of using clozapine first versus the currently approved strategy of using clozapine third, would cost $24,100 per additional QALY gained (see **Table 2**, column 3). Results of our subanalyses exploring the cost-

Table 2. Base Case Results

Strategy	Discounted Costs	Discounted Quality-Adjusted Life Years (QALYs)*	Cost-Effectiveness Ratio Versus Clozapine-Third Strategy	Cost-Effectiveness Ratio Versus Conventional Only Strategy
Conventional only	$509,200	14.51 QALYs*	–	–
Clozapine-third	$513,800	14.58 QALYs*	–	$64,400 / QALY*
Clozapine-first	$514,100	14.59 QALYs*	$24,100 / QALY*	$58,000 / QALY*

Note: * QALY = quality adjusted life year

effectiveness of strategies in settings where the current care involves only the use of conventional agents, even for treatment-resistant patients, are shown in **Table 2**, column 4. The clozapine-first vs. conventional only strategy would cost $58,000/QALY; the clozapine-third vs. conventional only strategy would cost $64,400/QALY.

Sensitivity Analyses

1-Way Sensitivity Analyses

In one-way sensitivity analyses (see **Table 3**), the cost-effectiveness ratio comparing clozapine-first vs. clozapine-third strategies was most sensitive to estimates of the rate of recovery from acute psychotic episodes on conventional antipsychotics and on clozapine; assigning the value most unfavorable to the clozapine-first strategy for either of these yielded ratios over $30,000/QALY. The analysis was also sensitive to the quality of life weight assigned to being recovered from psychosis, rates of TD on conventional antipsychotics, the cost of clozapine, the cost of inpatient hospitalizations, the discount rate, relapse rates on clozapine and conventional antipsychotics, and the cost of residential treatment, in descending order. The cost-effectiveness ratio was relatively insensitive to all remaining variables.

Probabilistic Sensitivity Analysis

When transition probabilities, costs, and utilities were allowed to vary simultaneously in the Monte Carlo simulation, the 25,th 50,th and 75th percentiles of the cost-effectiveness ratio of the clozapine-first compared with the clozapine-third strategy were $16,700, $23,500, and $31,100 per QALY gained, respectively.

Discussion

The FDA originally restricted clozapine use to only patients who failed two other antipsychotics, out of concern that using clozapine as a first-line agent would lead to greater loss of life, largely through death from agranulocytosis.[1-5] Contrary to this view, we found that employing clozapine as a first-line agent was no more hazardous and may actually lead to small gains in life expectancy and quality-adjusted life expectancy relative to waiting for two failures. This results from decreased likelihoods of suicide, treatment failure, and relapse on clozapine, as well as freedom from extrapyramidal side effects. These benefits outweigh the rare adverse consequences caused by agranulocytosis. The gains seen in quality-adjusted life expectancy are obtained at the acceptable costs of $24,100/QALY. This cost-effectiveness ratio is comparable to the ratios for many other commonly accepted medical interventions.[48] In health care systems where clozapine is currently never used even for treatment-resistant patients, employing it as a first-line agent also appears to lead to modest gains in QALYs at a fairly reasonable cost.

In all sensitivity analyses, using clozapine first continued to result in slightly higher quality-adjusted life expectancy when compared to using clozapine only after failure of two conventional agents. The cost-effectiveness ratio of the clozapine-first vs. the clozapine-third strategy was most sensitive to estimates of the efficacy of clozapine and conventional antipsychotics in producing recovery from acute psychotic episodes. For this reason, it is noteworthy that we used dischargeability from the hospital as our measure of recovery,[8] rather than improvement in symptom severity as in earlier studies.[18-29] Using this endpoint underestimates the advantage of clozapine over conventional antipsychotics because it does not account for the greater frequency of partial improvements observed for clozapine vs. conventional antipsychotics.[8]

The analysis was also sensitive to the quality of life weight assigned to recovery from psychosis. We conservatively assumed that recovery from psychosis led to the same quality-of-life with either clozapine or conventional antipsychotics, even though other investigators have found greater preferences in standard gambles[25] as well as higher patient satisfaction ratings[8] for clozapine as compared with conventional agents.

The probability of developing TD on conventional antipsychotics was another important parameter. Again, it is important to point out that we conservatively modeled TD to be a temporary condition lasting only 3 months rather than as the chronic form often encountered in clinical practice; in addition, we conservatively only considered tardive dyskinesia but not other extrapyramidal side effects from conventional antipsychotics, such as Parkinsonian symptoms, dystonias or akathisia.[11,39,43,49] Both assumptions are likely to have biased our results against the clozapine-first strategy.

Table 3. One-Way Sensitivity Analyses of the Most Influential Parameters on the Cost-Effectiveness Ratio Comparing Clozapine-First to Clozapine-Third Strategies

Variable	Range	Biased Toward Clozapine First ($/QALY)	Biased Toward Clozapine Third ($/QALY)
Prob. Recovering On Conventional Antipsychotic (%)	34.1-46.0	10,600	38,400
Utility of Being Recovered	1.0-0.6	18,900	36,200
Prob. Recovering on Clozapine (%)	48.9-36.9	17,400	32,600
Prob. TD on Conventional Antipsychotic (%)	1.7-0.9	17,500	30,600
Cost of Clozapine (425 mg/d) ($)	905-1509	17,900	30,200
Cost of Inpatient Psychiatric Hospitalization ($)	14,390-8634	17,900	30,200
Discount Rate (%)	0-5	18,000	29,100
Prob. Relapse on Clozapine (%)	5.9-10.1	18,200	28,400
Prob. Relapse on Conventional Antipsychotic (%)	10.4-15.5	21,900	27,400
Cost of Residential Treatment ($)	1520-2533	21,700	26,400

The fact that the model's results varied with the cost of clozapine is also important in light of clozapine's recent patent expiration and the availability of generic products. The price of generic clozapine has been declining and should continue to come down in the future, potentially making the use of clozapine as a first-line agent more economical. We also assumed weekly WBC monitoring for clozapine in our base case analysis, rather than the current practice of monitoring every 2 weeks after 6 months. All of these assumptions are likely to have biased our results against the clozapine-first strategy.

To our knowledge, this is the first study to quantitatively compare the strategy of using clozapine as a first-line agent to the current strategy of restricting clozapine use to only those who have failed at least two trials of other antipsychotics. Prior analyses have generally compared the cost-effectiveness of clozapine to conventional antipsychotics for the treatment of patients with exclusively treatment-resistant schizophrenia. While these have consistently shown that clozapine is cost-effective for treatment-resistant patients,[18-29] they have not addressed the larger question of managing treatment-sensitive as well as treatment-resistant patients.

These results have some limitations. First, some estimates were drawn from observational studies, introducing the possibility of confounding bias. For example, we used observational data[12-14] to estimate the suicide rates on clozapine and conventional neuroleptics because sample sizes in clinical trials or even meta-analyses were too small to generate stable estimates. Such estimates could be confounded by the fact that current clozapine users (who had to comply with weekly WBC monitoring to receive the drug), may be in a more stable clinical phase than either past users or non-users.[50] However, one recent randomized trial found significantly reduced suicidal behavior among clozapine users (although it compared clozapine to the newer atypical antipsychotic olanzapine rather than conventional neuroleptics).[15] Furthermore, our sensitivity analyses indicate that the decision to use clozapine as a first-line agent does not depend critically on a benefit on suicide for clozapine.

Second, even estimates drawn from randomized clinical trials may have limited internal and external validity. For example, medication non-compliance in clinical trials can attenuate the apparent efficacy of antipsychotic medications and affect cost-effectiveness analyses in unpredictable ways.[51] Furthermore, any attenuation due to non-compliance may have been differential between clozapine vs. conventional antipsychotics, because weekly WBC monitoring required of clozapine patients may enhance compliance. Non-compliance with WBC monitoring could itself lower costs and effectiveness of clozapine regimens; the net impact on cost-effectiveness ratios, while uncertain, may be lessened by recent reductions in FDA monitoring requirements. The generalizability of estimates from clinical trials to ''real-world'' practice is also unknown, due to the greater likelihood of non-compliance in typical settings.

Third, to avoid ''state explosion'', the model does not completely describe the range of health states that could be experienced by patients with schizophrenia. For example, clozapine and conventional antipsychotic users can experience other side effects from their medications that were not modeled as health states in our analyses.[43] However, our model does capture those side-effects that have been clearly established and are most burdensome (due to their prevalence and clinical seriousness). Furthermore, we conservatively did not model several potential benefits of clozapine, including improvements in: psychotic symptom severity that may be clinically important but not enough to lead to discharge from the hospital;[8] cognitive function;[52] medication compliance;[8] and non-lethal suicide attempts.[13,14,53]

Fourth, it was not possible to construct 95% confidence intervals for some of our parameter estimates due to the lack of information on their underlying variability. While we relied on conventions commonly employed under such circumstances (e.g., adding and subtracting 25% of base case estimates) to construct ranges for sensitivity analyses, we do not know how such ranges would relate to true 95% confidence limits. Furthermore, while our Markov model assumes constancy in parameter estimates, it is possible (but unknown) that transition probabilities, costs, and utilities change with time and the occurrence of clinical events. We believe the ranges employed in sensitivity analyses are sufficiently broad to contain the *average* in parameters experienced over the time horizon, however we cannot be certain.

Finally, clinicians and patients still face a critically important question about clozapine that this study cannot answer: what should the *preferred* first-line treatment be in schizophrenia? This question has become more pressing as newer atypical agents become widely available and used.[31] Unfortunately, we were unable to answer this question because there are insufficient head-to-head trials comparing clozapine to newer atypical antipsychotics in treatment-sensitive patients.[54-56] Trials completed to date leave open the possibility that clozapine may possess superior efficacy on several important clinical outcomes.[15,32] Clearly, additional data from large trials comparing clozapine to newer atypical agents in treatment sensitive patients are needed in the future. With publication of such results, the structure of the present analysis can be updated to shed light on this critically important question.

In summary, we found that using clozapine as a first-line agent vs. as a third-line agent, rather than leading to loss of life, actually leads to small gains in life-expectancy and quality-adjusted life-expectancy at the acceptable cost of $24,100/QALY. While results from this study do not shed light on whether clozapine should be the *preferred* first-line strategy, they do suggest that clozapine should not necessarily be confined to its role as a third-line agent. Both clinical and economic reasons appear to justify its addition to the armamentarium of *possible* treatments for treatment-sensitive as well as treatment-resistant schizophrenia.

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