The Business Case for Expanded Clozapine Utilization

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Objective: In most settings, less than 25% of patients with treatment-resistant schizophrenia receive clozapine, the only medication proven effective for treatment-resistant schizophrenia. Therefore, a business case analysis was conducted to assess whether increasing clozapine utilization for treatment-resistant schizophrenia in a health care system would result in direct health care cost savings.

Methods: Veterans with treatment-resistant schizophrenia who were treated in the Veterans Health Administration (VHA) were studied. Treatment response, suicides, adverse drug reactions (and associated mortality), and effects on inpatient hospitalization related to clozapine were derived from a systematic review of published studies. A one-factor sensitivity analysis and a probabilistic sensitivity analysis (PSA) with Monte Carlo simulation were conducted to calculate the cost-benefits of increased clozapine utilization.

Results: Despite monitoring costs, in the base case analysis, the VHA would save $22,444 per veteran with treatment-resistant schizophrenia over the first year of clozapine therapy, primarily from 18.6 fewer inpatient days per patient. If current utilization was doubled, and 50% of those veterans continued clozapine treatment for one year, VHA would save an estimated $80 million. Cost savings were most sensitive to the proportion of treatment-resistant patients who received clozapine, decrease in inpatient days, cost of inpatient stays, clozapine response rate, and number of patients with treatment-resistant schizophrenia. In the PSA, initiation of clozapine for all VHA patients with treatment-resistant schizophrenia who were not currently treated with clozapine would save at least $290 million in 95% of simulations.

Conclusions: Increased clozapine utilization would result in net cost savings for the VHA.

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Clozapine is the only treatment that has been proven effective for treatment-resistant schizophrenia (1–11) and the only treatment approved by the U.S. Food and Drug Administration (FDA) to decrease suicidal behavior associated with schizophrenia (7). However, clozapine is associated with significant adverse drug reactions (ADRs), requiring compliance with an FDA-mandated risk mitigation and evaluation strategy program (7). Given the complexity of the program—which requires patient, prescriber, and pharmacy registration; weekly blood draws; and seven-day fills for the first six months of therapy—clozapine is prescribed for only a minority of patients with treatment-resistant schizophrenia (12–17).

Despite evidence demonstrating clozapine's benefits, use of clozapine in the United States has steadily declined since the introduction of other second-generation antipsychotics to the U.S. market (12,13). Within the Veterans Health Administration (VHA), 4% of patients with schizophrenia receive clozapine (13). Low clozapine utilization is also reported in non-VHA and international treatment settings (11,14–16). Considering that 20% to 30% of patients have treatment-resistant schizophrenia, the low rate of utilization of clozapine implies that 82% to 88% of patients with treatment-resistant schizophrenia are receiving less effective antipsychotics.

Given clozapine's unique effectiveness for treatment-resistant schizophrenia and its potential to decrease suicidal behaviors and utilization of more costly forms of care, increasing clozapine utilization could lead to significant cost savings, despite increased monitoring and contact with the health care system. Therefore, we conducted a cost-benefit analysis with data obtained from a medical literature review to simulate potential cost savings associated with increasing clozapine utilization within the VHA. The hypothesis was that potential cost savings, mostly from decreased inpatient hospital days, would constitute a case for expanding clozapine utilization, even if achieving such a goal entailed considerable costs and effort.

METHODS

Model Design

We developed a simulation on the basis of data from the medical literature to estimate costs associated with varying degrees of clozapine utilization. The decision model is a tree structure comparing the choice of whether or not to use

clozapine for a treatment-resistant patient at a single decision node over a one-year time horizon, calculated from the perspective of the VHA (18). In the clozapine arm, subsequent branch points were event nodes that represent likelihood of response, risk of completed suicide, and risk of serious ADRs resulting in clozapine discontinuation (Figure 1). In the clozapine arm, nonresponse was assumed to lead to clozapine discontinuation. We modeled only serious ADRs (agranulocytosis, seizures, diabetic ketoacidosis, myocarditis, and ileus) that have been attributed to clozapine use (7). [The decision tree for ADRs is available as an online supplement to this article.]

In the nonclozapine arm, suicide risk was modeled at a single branch point, and we assumed that there would be no ADRs, even though other medications cause ADRs. This is a simplifying assumption, but a conservative model was chosen to decrease the likelihood of overestimating the benefits of clozapine treatment. Costs of inpatient and outpatient psychiatric care, laboratory monitoring, and health care expenditures related to ADRs were incorporated into the clozapine arm. Differential mortality risks from completed suicides between the clozapine and nonclozapine arms and aggregate risks of mortality from clozapine-related ADRs were calculated.

This study was exempted from review by the Edith Nourse Rogers Memorial Veterans Hospital's Institutional Review Board.

Model Inputs

Response to clozapine. We conducted a systematic literature search of MEDLINE articles indexed between January 1, 1985, and June 30, 2015, for studies using the terms "clozapine" AND "refractory schizophrenia" OR "treatment resistant" OR "resistant schizophrenia." Thirty-nine articles were evaluated for number of persons given clozapine and clinical response rate (4,19–56). If these values could not be ascertained from the text or if the subjects were under 18 years of age, the article was excluded. Response was most commonly defined as a 20% improvement in baseline score on the Brief Psychiatric Rating Scale, but inclusion of an article was not conditional on this definition. Of the 39 identified articles, 31 articles comprising 2,571 clozapine patients were included (4,19–45,47–49) [see online supplement]. We calculated a pooled clozapine response rate of 51%.

Suicide rate. Completed suicide rate was calculated as the product of the annual suicide rate for the U.S. general population ages 35–64, the standardized mortality ratio from suicide for schizophrenia, and a published hazard ratio of suicide for male veterans with schizophrenia (57–60). The effect of clozapine on suicide risk was determined on the basis of a meta-analysis of five studies that calculated the relative risk of completed suicide associated with use of clozapine. The relative risk of completed suicide was 2.90 among patients who did not use clozapine compared with those who used clozapine (61). For this model, reduction in the risk of suicide was applied only among clozapine responders; nonresponders were assumed to have a similar risk of suicide as patients receiving nonclozapine antipsychotics.

Clozapine-related ADRs. Pooled risks and mortality of the clozapine-related ADRs were calculated from studies identified through the literature review and the clozapine-prescribing information (7,62–64). A pooled risk of clozapine-related seizures and subsequent risk of discontinuation were calculated from an analysis of the clozapine patient management system database (64).

Costs of treatment. Costs for the first year of clozapine treatment were determined to be the cost of laboratory monitoring and follow-up visits plus the VHA cost of clozapine tablets. On the basis of current guidelines for monitoring, there are a total of 39 visits over the course of one year of treatment (weekly for six months and biweekly for the next six months) (7). We used the pricing schedule used by the Centers for Medicare and Medicaid Services for the 2015 CPT code for a complete blood cell count with differential cell count and for the evaluation and management code for a level II visit with a psychiatrist (65). Patients were assumed to be reimbursed $20 for travel costs by VHA for each follow-up visit. Clozapine costs in the base case were for a total daily dose of 600 mg, based on 2015 VHA pricing of 41 cents for a 100-mg tablet.

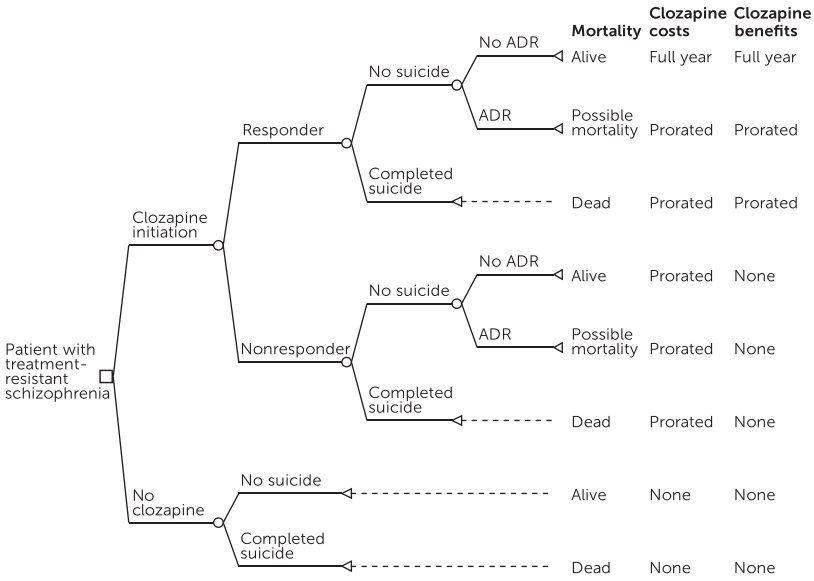
Costs of ADRs. The estimated cost of the ADRs was the sum of annual direct health care costs (prescriptions, inpatient treatment, emergency services, outpatient treatment, and office-based medical visits). Adults with relevant three-digit *ICD-9-CM* codes and Clinical Classification Software codes were identified through examination of the Medical Expenditure Panel Survey from 2002 to 2011 for condition-related annual health care expenditures (66). For diabetic ketoacidosis, costs were for a single inpatient hospitalization rather than yearly costs (67).

Inpatient psychiatric stays and costs. The length of inpatient stay was calculated from a pooled, random-effects meta-analysis of seven studies identified in the systematic review (33,34,36,38,39,68,69) [see online supplement]. These studies evaluated the impact of clozapine therapy on hospital days, using either a prepost comparison or a comparison between hospital days for intervention and control patients. The cost of an inpatient stay at a VA hospital was estimated at $1,414 per day (13).

Treatment-eligible population. In 2009, a total of 87,000 veterans had schizophrenia or schizoaffective disorder (13). Although 20% to 30% of patients are reported to have treatment-resistant schizophrenia, we assumed that 20% of patients, an estimated 18,000 veterans, had treatment-resistant

schizophrenia (1). Assuming that the 3.6% of veterans with schizophrenia already treated with clozapine had treatment-resistant schizophrenia, we estimated an additional 14,400 veterans with treatment-resistant schizophrenia would be eligible for a clozapine trial.

FIGURE 1. Outcomes of a decision model involving whether to initiate clozapine for a patient with treatment-resistant schizophrenia[a]



[a] ADR, adverse drug reaction

Cost Reporting

For each parameter, costs that were not already in 2015 U.S. dollars were inflated to 2015 U.S. dollars by calculating the rate of medical inflation from the Consumer Price Index (CPI) between the year in which the parameter was reported and 2014 (last available year of the CPI) and then adjusting again by the average yearly rate of medical inflation from 2010 to 2014 (70).

Analysis

This analysis was a cost-benefit model, comparing costs and monetizing benefits associated with clozapine use and nonuse in treatment-resistant schizophrenia. The deterministic base case model used the parameter estimates for the model inputs detailed above to determine the difference in costs for treatment-resistant schizophrenia between clozapine treatment and nonuse of clozapine. In the clozapine arm, the costs of treatment, ADRs, and inpatient stays were summed. In the nonclozapine arm, it was assumed that ADRs did not occur and medications had no costs, so the costs reflected inpatient stays. Mortality was estimated by the effect of clozapine on suicide among veterans and anticipated mortality from serious ADRs (61–63). The business case for clozapine was broadened by multiplying the results over the treatment-eligible population within the VHA.

Several assumptions were made for model variability. Costs of expenditures directly attributable to clozapine use (prescriptions, laboratory monitoring, office visits, and treatment of serious ADRs) were not included in the control arms. Health care expenditures unrelated to clozapine effects were assumed to be identical in the two arms to prevent needlessly complicating the model; these expenditures included metabolic monitoring, which is recommended for all patients on antipsychotics. Benefits of reduced inpatient stay and diminished incidence of completed suicide were applied only for clozapine responders. Costs of clozapine treatment were incurred for the entire year for clozapine responders and were prorated until day of discontinuation for nonresponders. All costs for persons who died by suicide were curtailed at the day of suicide. ADR costs were prorated from the day on which the ADR occurred until the end of the year, with the exception of diabetic ketoacidosis, which was assumed to be a single event. In the base case deterministic model, suicide, clozapine discontinuation due to nonresponse, and ADRs occurred at six months, the midpoint of the year (day 183). Among clozapine responders, the ADRs were assumed to lead to discontinuation, except seizures, in which case we used published rates of discontinuation of clozapine following a seizure to estimate the proportion of patients who would continue clozapine (64). For clozapine nonresponders, all ADRs were assumed to result in drug discontinuation.

To incorporate uncertainty, one-factor sensitivity analyses and a probabilistic sensitivity analysis (PSA) with Monte Carlo simulation were calculated (71). In the factor analysis, we varied the range of input parameters by 20% in each direction from the base case, except the proportion of treatment-resistant schizophrenia patients initiated on clozapine, which were varied from 20% to 80%. We then evaluated the relative influence of high and low values for each input on cost savings for the health care system. For the PSA, method of moments were used to fit probability parameters on beta distributions, relative risk and hazard ratios on log normal distributions, and event days (ADRs, clozapine discontinuation, and suicide). Fixed costs (lab monitoring, veteran travel, and psychiatrist visits) were varied on uniform distributions. Gamma distributions were used to fit aggregate ADR costs, and Poisson distributions were used to fit inpatient days (Table 1). Random numbers generated output values within distributional assumptions. Simulated cost outcomes were determined for the entire health care system, with 1,000 replications each for initiation of clozapine among 20%, 40%, 60%, and 80% of patients with treatment-resistant schizophrenia. The last of these proportions would equate to 100% clozapine use because it would be added to the current rate of use of clozapine for treatment-resistant schizophrenia, which is approximately 20%. Simulations and analysis were performed by using Excel 2010 and Stata, version 13, software packages.

TABLE 1. Adjustment of base case values during sensitivity analyses of the cost-benefits of increased clozapine utilization among veterans with treatment resistant schizophrenia[a]

Variable	Base case	SD	Distribution	Notes
Veterans with treatment-resistant schizophrenia	18,000		Uniform	2009 VHA estimate of ~90,000 patients with schizophrenia × 20% rate of treatment-resistant schizophrenia (13)
Proportion initiated clozapine treatment	.20		Uniform	Assumption
Probability of clozapine response	.510	.01	β	Pooled meta-analysis of 31 studies (4,19–45, 47–49) [see online supplement]
Probability of completed suicide[b]	.003		β	U.S. suicide rate for ages 35–64 × SMR for suicides among persons with schizophrenia × HR for suicides among male patients with schizophrenia (57–60)
Completed suicide rate given clozapine response	.34	.8	Log normal	Prevention of suicides with clozapine (61)[c]
Probability of ADR (clozapine arm only)				
Agranulocytosis	.005	.0002	β	Calculated from Cohen et al., 2012 (63)
Myocarditis	.0001	.000	β	Calculated from Cohen et al., 2012 (63)
Ileus	.004	.0004	β	Calculated from Cohen et al., 2012 (63)
Seizures	.032	.003	β	Calculated from Cohen et al., 2012 (63)
Diabetic ketoacidosis	.0001	.000	β	Calculated from Cohen et al., 2012 (63)
Probability of discontinuation of clozapine due to seizures	.352	.046	β	Calculated from Pacia and Devinsky (64)
Probability of mortality due to ADR	.28	.28	β	Calculated from Cohen et al., 2012 (63)
Myocarditis				
Agranulocytosis	.03	.007	β	Calculated from Cohen et al., 2012 (63)
Ileus	.20	.036	β	Calculated from Cohen et al., 2012 (63)
Diabetic ketoacidosis	.03	.04	β	Calculated from Cohen et al., 2012 (63)
Fixed costs ($)[d]				
Lab monitoring (event)	10.58		Uniform	WBC; CPT G0306 (CMS 2015 Lab Diagnostic Fee Schedule, global, nonfacility) (64)
Psychiatrist visit	43.98		Uniform	CPT 99212 (CMS 2015 Physician Fee Schedule, global, nonfacility) (64)
Veteran travel (event)	20.00		Uniform	Assumption
Clozapine treatment (day)	2.46		Uniform	100-mg tablet, 600 mg/day (VHA VISN 1 costs)
Inpatient stay (day)	1,413.70		Uniform	2009 VHA estimate (2015 $)
Cost for ADR (2015 $)				
Seizures (year)	1,621.62	245.75	γ	MEPS 2002–2011 for adults (*ICD-9* code 345) (66)
Myocarditis (year)	3,695.89	934.70	γ	MEPS 2002–2011 for adults (*ICD-9* code 422) (66)
Agranulocytosis (year)	2,428.31	1,641.52	γ	MEPS 2002–2011 for adults (*ICD-9* code 288) (66)
Ileus (year)	6,796.33	1,234.79	γ	MEPS 2002–2011 for adults >18 (*ICD-9* code 560) (66)
Diabetic ketoacidosis (single hospitalization)	20,141.34	20,415.43	γ	(67)
Day of suicide	183		Uniform	Assumption
Day of discontinuation of clozapine	183		Uniform	Assumption
Day of ADR (clozapine arm)	183		Uniform	Assumption
Inpatient days	138		Poisson	Pooled analysis of 7 studies (33,34,36,38,39,68,69) [see online supplement]
Reduction in inpatient days among clozapine responders	−37[e]		Poisson	Unstandardized mean difference in inpatient days of 7 studies (33,34,36,38,39,68,69) [see online supplement]

[a] The base case used assumed or estimated mean values. SDs were used to calculate gamma (γ) and beta (β) distributional parameters for probabilistic sensitivity analysis. Abbreviations: ADR, adverse drug reaction; CMS, Centers for Medicare and Medicaid Services; HR, hazard ratio; MEPS, Medical Expenditure Panel Survey; RR, relative risk; SMR, standard mortality ratio; VISN, Veterans Integrated Service Network; and WBC, white blood cell count

[b] The probability of suicide among veterans with treatment-resistant schizophrenia was a function of three individual parameters with distributional properties of mean and standard deviation. The SD variance was calculated from product of component inputs (SMR, HR, and incidence).

[c] The suicide rate for clozapine was calculated as the reciprocal of the rate of suicide prevention in the article by Hennen and Baldessarini (61).

[d] Fixed costs did not have an SD but were varied on uniform distributions with a range of ±20%.

[e] The SD was the square root of the mean for Poisson distribution.

RESULTS

Cost Savings

If 20% of veterans with treatment-resistant schizophrenia initiated clozapine, the one-year costs to the VHA would decrease by a mean of $22,444 per patient treated with clozapine. Savings were driven primarily through an average reduction of 18.6 inpatient hospital days. If current utilization was doubled and 50% of those veterans continued clozapine treatment for one year, the VHA would accrue an estimated cost savings of $80 million (Table 2).

TABLE 2. Simulated outcomes from doubling baseline rates of clozapine utilization at the VHA for one year[a]

Outcome	Base case	Simulated outcome (percentile)		
		Mean	5th	95th
Aggregate cost and utilization				
Cost ($)				
Control arm	700,410,000	695,541,000	633,082,000	757,851,000
Clozapine arm	619,613,000	615,697,000	560,652,000	671,316,000
Cost savings ($)	80,797,000	79,845,000	72,406,000	87,685,000
Inpatient days				
Control arm	495,000	492,000	447,920	536,000
Clozapine arm	429,000	426,000	388,000	464,000
Inpatient days saved	67,000	66,000	60,000	72,000
Clozapine responders	1,787	1,794	1,629	1,964
Adverse drug reaction (ADR)[b]				
Seizures	116	115	94	137
Agranulocytosis	16	16	10	23
Myocarditis	<1	<1	0	1
Ileus	16	16	9	23
Diabetic ketoacidosis	<1	<1	0	2
Mortality				
Suicides (control arm)	11	11	6	17
Suicides (clozapine arm)	8	8	3	12
Deaths due to ADRs				
Agranulocytosis	<1	<1	0	2
Myocarditis	<1	<1	0	1
Ileus	3	3	1	6
Diabetic ketoacidosis	<1	<1	0	1

[a] Estimates are incremental costs, ADRs, and mortality associated with doubling estimated current clozapine use (deterministic base case analysis). Results are from the probabilistic simulation of incremental costs of clozapine initiation (clozapine arm) and noninitiation (control arm) associated with initiating clozapine for an additional 20% of the estimated 18,000 (±10%) veterans with treatment-resistant schizophrenia who were not currently receiving clozapine.

[b] Clozapine arm only. Seizures were assumed to be nonfatal.

ADRs

An additional 743 serious ADRs would occur in year 1 if all veterans with treatment-resistant schizophrenia who had previously not been treated with clozapine initiated clozapine treatment. If only 20% of those veterans began treatment with clozapine, an additional 149 serious ADRs would occur (Table 2).

Deaths

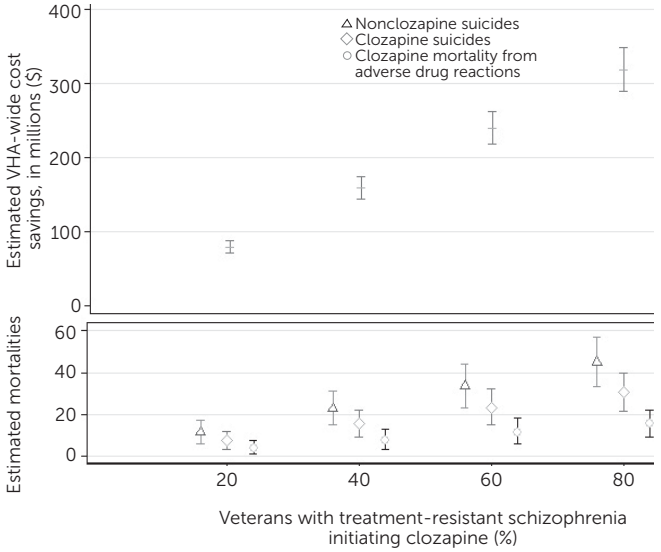
If all veterans with treatment-resistant schizophrenia who had not been treated with clozapine later initiated clozapine, 19 suicides would be averted annually, and there would be a total of 18 additional deaths, three due to clozapine-related agranulocytosis and 15 due to ileus. If only 20% of veterans with treatment-resistant schizophrenia who had not previously initiated clozapine began treatment with clozapine, there would be three deaths due to clozapine-related ADRs and three fewer suicides in the clozapine group versus the nonclozapine group. Greater increases in clozapine use would lead to more lives saved by suicide prevention than lives lost to clozapine-associated ADRs (Figure 2).

Sensitivity Analysis

One-way sensitivity analysis was performed, varying each of the model inputs across a plausible range to evaluate the input's influence on our findings. Cost savings were most sensitive to changes in the proportion of patients with treatment-resistant schizophrenia who received clozapine (92% of the swing in range of costs), reduction in inpatient days (2%), cost of inpatient stay (2%), rate of response to clozapine (2%), and number of patients with treatment-resistant schizophrenia (2%) (Figure 3). Costs associated with laboratory monitoring, ADRs, outpatient visits, and travel had negligible impact on costs for the payer. Probabilistic sensitivity analysis confirmed that increasing the number of patients with treatment-resistant schizophrenia receiving clozapine would result in incremental cost savings. Assuming a baseline rate of 20% for clozapine utilization, cost savings increased to $323,188,000 when 100% of patients with treatment-resistant schizophrenia were prescribed clozapine.

Figure 2 shows the cost implications of initiating clozapine for 20% to 80% of patients with treatment-resistant schizophrenia (representing 100% utilization at beginning of year 1, including current users). A relatively modest change, doubling utilization from 20% to 40% of eligible patients, would lead to cost savings of more than $80 million in the first year of treatment. In 95% of simulations, increasing clozapine utilization from 20% to 40% of eligible patients saved a minimum of $72 million in the first year. Initiation of clozapine for all VHA patients with treatment-resistant schizophrenia who were not currently treated with clozapine would save at least $290 million in 95% of simulations.

FIGURE 2. Estimated one-year VHA-wide savings and mortality associated with incremental gains in clozapine utilization among veterans with treatment-resistant schizophrenia[a]



[a] Bars indicate mean, 5th, and 95th percentiles from 1,000 simulations for each incremental increase of 20%.

DISCUSSION

Clozapine has repeatedly demonstrated superiority to other antipsychotics for treatment-resistant schizophrenia, but it is underutilized. Therefore, we simulated the effects of increasing clozapine utilization for patients with treatment-resistant schizophrenia. Doubling the proportion of patients with treatment-resistant schizophrenia who received clozapine from 20% to 40% would save $80 million for the VA, without considering any value accruing to patients from improved outcomes. In addition, despite the much-feared adverse effects of clozapine, the increase in ADR-related mortality associated with clozapine would be more than offset by suicide prevention.

The benefits of increased clozapine utilization may have been underestimated because of several assumptions. First the model assumed that 20% of patients with schizophrenia have treatment-resistant schizophrenia, although many studies have estimated a rate as high as 30% (1). Second, the costs of clozapine treatment are substantially higher in the first year compared with later years because of a need for more office visits and laboratory monitoring. After the first year, the continued costs of clozapine treatment are more similar to those of other antipsychotics, but the benefits of clozapine treatment continue to accrue. Third, this model assumed that treatment with other antipsychotics did not result in serious ADRs or include prescription or other treatment costs. Thus it is possible savings could be higher than reported in this study.

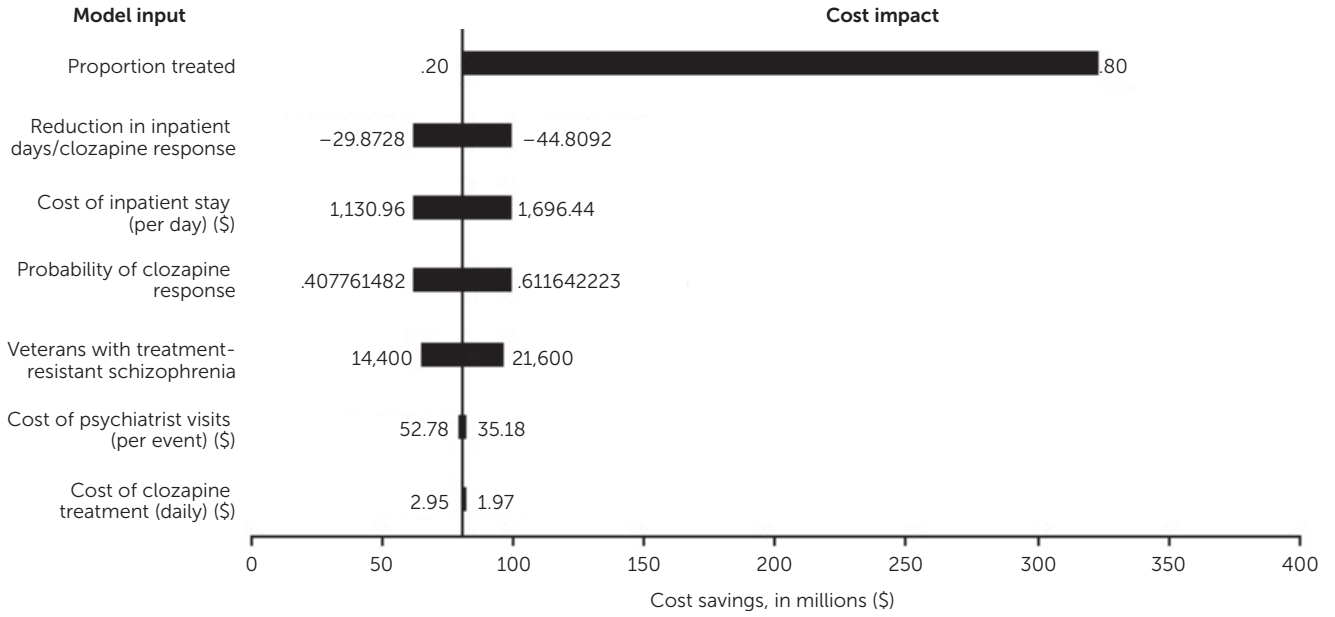
Our analyses had several important uncertainties. First, it was difficult to estimate the incidence and costs of obesity and diabetes risk and the expected increased risk in cardiovascular mortality and morbidity associated with use of clozapine. Some comparator agents have similar risks, whereas most have substantially lower risks than clozapine (72). In addition, studies have reported mixed effects of clozapine on mortality (73–75). As such, cardiometabolic ADRs were not included in the analyses. Second, it should be remembered that extrapolation of cost savings to subsequent years and to use outside the VHA is uncertain. Third, some of the studies providing evidence for clozapine benefits were conducted years ago and thus may be less relevant to current practice. Finally, the base model assumed a reduction of 30 inpatient days in the first year. Although that may seem extreme in an era of shortened hospitalizations, the average length of stay for schizophrenia both within and outside the VHA in 2009 and 2011 was approximately 21 days, and patients with treatment-resistant schizophrenia averaged three hospitalizations per year (13,76). In addition, studies indicate that more severe illness, as would be expected with treatment-resistant schizophrenia, further increases the length of stay (76). Thus it is reasonable to assume that clozapine would be associated with 30 days of inpatient hospitalization. Varying the analyses by limiting the number of days of hospitalization avoided to seven still resulted in cost savings [see online supplement].

This study had important strengths. A number of underlying assumptions suggest that, if anything, benefits of increased clozapine utilization have been underestimated. In addition, much is known about the improved outcomes, adherence, and persistence rates associated with clozapine treatment (75,76). However, the study also had some limitations. First, all the data were not from the VHA or specifically related to treatment-resistant schizophrenia. For example, the suicide rate was not based on rates for schizophrenia populations with treatment-resistant disease, given the lack of data on suicide among patients with treatment-resistant schizophrenia. Second, rates of response, ADRs, and costs associated with use of clozapine were based on the published literature and may not accurately reflect real-world systems. Third, dispensing costs were not included, given that we found no estimates that included the added cost of maintenance and oversight of the VHA clozapine registry.

Clozapine monitoring guidelines have recently changed. It is unlikely that these changes will have a significant impact on cost of monitoring, but the possibility cannot be excluded. In addition, monitoring of clozapine serum concentrations is recommended by some guidelines. Because clozapine serum concentrations are not routinely monitored, we excluded these costs from our analyses. If completed, such monitoring would be expected to increase clozapine costs.

It is important to note the circumscribed nature of the study. This study was not a cost-utility analysis and, therefore, did not formally model patient-related outcomes, such as health-related quality of life. Instead, we opted to conduct a simpler business case analysis from the VHA perspective, including direct health care costs and veterans' travel costs

FIGURE 3. Effects of varying the model inputs on the cost of clozapine care[a]



[a] Input parameters were varied from the base case by 20% in each direction, except proportion of patients with treatment-resistant schizophrenia who were treated with clozapine, which varied from 20% to 80%. Reduced inpatient days were prorated for the clozapine response rate probability. Rates of adverse drug reactions (ADRs), suicide, clozapine discontinuation, costs of ADRs, and laboratory monitoring had smaller impacts.

but excluding indirect costs, such as caregiver time and missed work. It should be noted that the value to society from increased clozapine utilization for treatment-resistant schizophrenia would greatly exceed the cost savings we reported here because patients and, presumably, their families prefer that the symptoms of schizophrenia be well controlled (77). However, payers are likely most responsive to a business case analysis, which is why we chose this approach.

In a separate study, we found that some relatively straightforward strategies were associated with higher clozapine utilization within the VHA (78). Among these are having a dedicated clozapine clinic; ensuring that the clinic has sufficient capacity to accommodate all patients with treatment-resistant schizophrenia and adequate staffing levels by nonphysicians, including registered nurses and pharmacists; and providing transportation to appointments for patients using clozapine. Although these strategies are allowable under VHA rules and regulations and are currently used at some sites, they are not without cost.

It is hoped that this study provides an impetus to make these relatively straightforward, if not inexpensive, changes. Extrapolating from our findings, an average-sized VHA site (managing 700 schizophrenia patients) could expect to have 140 patients with treatment-resistant schizophrenia. Increasing the proportion of patients with treatment-resistant schizophrenia who are treated with clozapine from 20% to 40% would save the facility more than $625,000 in the first year alone. It is difficult to imagine that the cost of implementing our recommendations could approach this figure. Thus, even a modest increase in clozapine utilization, achieved at a very high cost, could still result in a net cost savings for the VHA.

CONCLUSIONS

This study found that modest increases in clozapine utilization could yield significant cost savings. It is very unusual to have the opportunity to save money while improving patient outcomes, particularly in such a vulnerable population. Our results suggest that the VHA should strongly consider initiatives, possibly based on practices already used by high-performing sites, to substantially increase clozapine utilization for treatment-resistant schizophrenia.

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