

## Implications of an SSRI Generic Step Therapy Pharmacy Benefit Design: An Economic Model in Anxiety Disorders

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### **Abstract**

As the antidepressant market continues to expand, it is important for healthcare decision makers to develop clinically and economically sound drug benefit designs. As such, the purpose of this study was to determine the economic implications of a generic step therapy (GST) formulary compared with an open formulary for selective serotonin reuptake inhibitors (SSRIs) in patients with anxiety disorders. A model simulating the SSRI treatment patterns of patients diagnosed with an anxiety disorder in a hypothetical health plan with 1 million members was developed. Treatment options were generic SSRI agents (ie, fluoxetine, paroxetine immediate release, and citalopram) and branded SSRI agents (ie, sertraline, paroxetine controlled release, and escitalopram). After treatment initiation, patients could achieve 180 days or more of continuous therapy with no evidence of therapy change, achieve less than 180 days of therapy with no evidence of therapy change, or have a change in therapy.

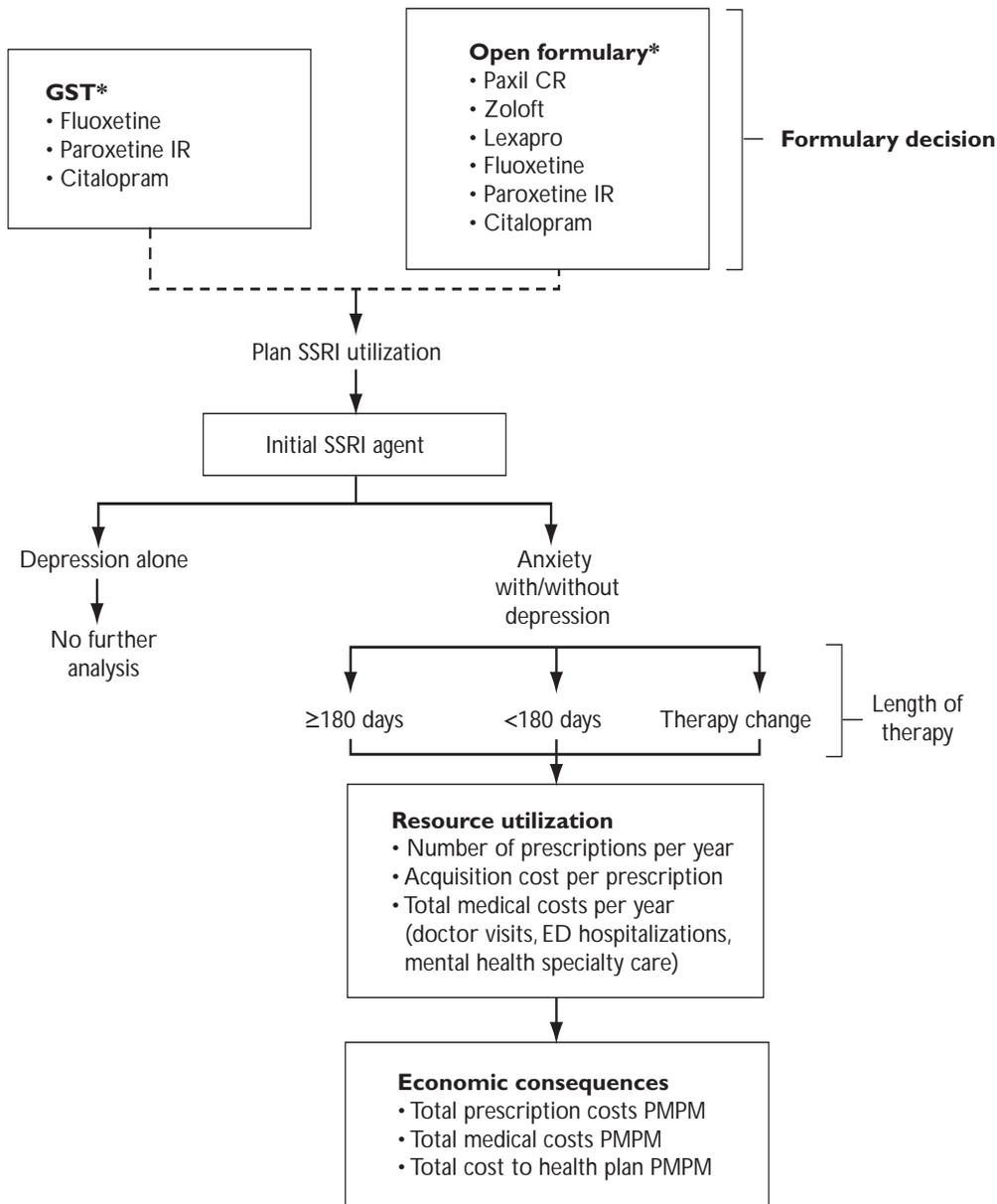
Consequently, patients incurred differential average annual medical and prescription costs. Model probabilities and costs were estimated from published literature and database analyses. The GST formulary resulted in a greater frequency of therapy change than the open formulary (41.3% vs 36.8%) and a lower frequency of continuous therapy for at least 6 months (25.3% vs 29.8%). Costs of SSRI medication were lower for the GST formulary than for the open formulary (\$11.6 million vs \$14.8 million). Medical costs were considerably greater for the GST formulary than for the open formulary, however (\$178.7 million vs \$174.9 million, respectively), with a total cost of \$190.3 million for the GST formulary versus \$189.6 for the open formulary. The incremental cost of implementing a GST formulary over 1 year was \$684 360, or \$0.06 per member per month. A sensitivity analysis indicated that the model was most sensitive to changes in the cost of SSRI drug therapy and the average annual medical costs for patients with evidence of therapy change. The results of this model indicate that implementing

a GST formulary for SSRIs in patients with anxiety disorders may be associated with an increased amount of therapy change and early treatment discontinuation, resulting in an overall cost increase to a health plan.

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Increased awareness of depression and the development of more tolerable agents have fueled the expansion of the antidepressant market, which currently exceeds \$20.3 billion annually.<sup>1</sup> The introductions of generic immediate-release (IR) paroxetine and citalopram along with new market entries, such as controlled-release (CR) paroxetine, escitalopram, and duloxetine, create challenges for formulary decision makers when choosing a clinically appropriate cost-effective therapy. As employers and health insurance providers consider ways to manage their antidepressant formularies, there are various questions that must be addressed, such as: Are there clinical differences between the selective serotonin reuptake inhibitor (SSRI) agents? Are there differences in the range of indications for which SSRIs are approved? Current strategies for managing antidepressant costs include tiered benefits, mandated generic substitutions, or required documentation of medical necessity, which have been derived from the premise that all antidepressants are equally efficacious and tolerable across all indications.<sup>2</sup> A cost containment design that emphasizes this premise is a generic step therapy (GST) prescription formulary, in which a patient requiring antidepressant treatment must first begin with a generically available product. However, although these

**Figure 1.** Model Treatment Pathway Framework



\*During the time of this model conceptualization, citalopram became available generically and thus was included in both the GST and the open formulary.

CR indicates controlled release; IR, immediate release; SSRI, selective serotonin reuptake inhibitor; ED, emergency department; PMPM, per member, per month; GST, generic step therapy.

approaches may decrease antidepressant drug costs, they fail to account for differences in the tolerability of these agents, which may substantially affect the number of patients that remain on therapy for an adequate period of time to achieve remission.<sup>3</sup>

Studies have shown that tolerability differs across the SSRI agents, with some of the newer branded available agents having increased tolerability over older generically available products. For example, 14% of patients reported nausea with paroxetine CR

**Table 1.** Plan/Utilization Assumptions of Model

Parameter	Model assumption/value
Plan population	1 million members
Members who receive antidepressants (%)	5.9
Patients with AD who receive SSRIs (%)	68
Total SSRI population	40 120
SSRI population treated for anxiety (%)	80
SSRI population treated for anxiety	32 096
SSRI market share, open formulary (%)	
Fluoxetine	20.2
Paroxetine IR	12.8
Citalopram	10.6
Sertraline	27
Paroxetine CR	8.5
Escitalopram	21

AD indicates antidepressant; SSRI, selective serotonin reuptake inhibitor; IR, immediate release; CR, controlled release.  
 Sources: References 11-14.

compared with 23% with paroxetine IR.<sup>3</sup> Rates of treatment discontinuation and therapy change are also different across the SSRIs, which is likely associated with the differences found in tolerability.<sup>4,5</sup> These findings are important because the initiation of a GST formulary may increase the percentage of patients requiring a therapy change or discontinuing therapy early due to tolerability issues. This may be especially true in patients with anxiety disorders, a prevalent group of disorders commonly treated with SSRIs and often comorbid with depression.<sup>6,7</sup> However, there is little comparative literature on antidepressant treatment outcomes in this population.

Because both therapy change and early discontinuation have been associated with an increased risk of relapse or recurrence in patients with anxiety and/or depression, these findings raise concern over the applicability of restrictive formulary designs.<sup>8,9</sup> The inability to select a therapy that has demonstrated improved efficacy or tolerability may increase the risk of patient nonadherence, consequently increasing the risk of relapse or recurrence and potentially offsetting any pharmacy cost savings from the restrictive drug formulary.<sup>5,10</sup> As such, the purpose of this study was to evaluate the

economic implications of a GST formulary compared with an open formulary, allowing for first-line branded agents, on SSRI agents in patients with anxiety disorders in a simulated health plan population.

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**METHODS**

To evaluate the economic impact of a GST formulary policy, a conceptual framework was constructed to simulate the pharmacologic treatment pathway of patients diagnosed with anxiety in a hypothetical health plan. As illustrated in **Figure 1**, this framework incorporates differential rates of diagnoses, length of therapy, and antidepressant therapy change rates for each SSRI agent available, as well as all relevant medical and pharmacy resource utilization from a health plan formulary perspective. A model was then developed to estimate the total medical and pharmacy costs of therapy and was run simultaneously and independently for each formulary.

Using literature-based and market research sources as listed in **Table 1**, the model identifies the proportion of patients within a health plan population who newly initiate therapy with an SSRI agent over 1 year. The model pathway displayed in **Figure 1** assumes that each patient within a health plan's population who is prescribed an SSRI agent is being treated for either depression alone or anxiety with or without comorbid depression. However, patients with depression alone were not included in further analysis and only patients with anxiety and comorbid depression or anxiety disorders alone were analyzed in the model simulation. The distribution of patients receiving each agent is determined based on an average hypothetical plan's market share distribution of the SSRI agents, with base case market shares obtained from VONA Data Management in this model (shown in **Table 1**).<sup>14</sup> The market share of the generically available SSRI agents for the GST formulary was determined by assuming similar patterns of distribution as for the open formulary; that is, that fluoxetine would have the greatest market share (45%), followed by paroxetine IR (30%) and citalopram (25%). The model then assumes

that for both formulary policies, patients will experience continuous treatment lasting 180 days or longer in accordance with national treatment guidelines, discontinue treatment early (<180 days of treatment), or have a therapy change, defined as either a switch (discontinuation of an index medication accompanied by the initiation of a new agent), short-term augmentation (an overlap of >30 days but <60 days between the index medication and a new medication), or long-term augmentation (overlap of an index medication with another anti-anxiety agent for at least 60 days).<sup>15,16</sup>

Probabilities from published literature and database studies were used to determine the distribution of patients into each treatment cohort.

**Model Inputs**

Inputs for this analysis were obtained from published literature and retrospective database studies. Inputs for the sequential pathway are displayed in **Table 2** and inputs for the resource utilization are detailed in **Table 3**. Additional model inputs were derived from the Red Book 2005.<sup>18</sup> Cost values are shown in 2004 US dollars.

**Table 2.** Distribution Into Patterns of Utilization

SSRI agent	Therapy change (%), independent of LOT		
Fluoxetine	43.9		
Paroxetine IR	38.3		
Citalopram	40.3		
Sertraline	35.0		
Paroxetine CR	30.8		
Escitalopram	31.8		
SSRI agent	LOT (%)		
	180 days	<180 days	
Fluoxetine	45.4	54.6	
Paroxetine IR	40.2	59.8	
Citalopram	42.7	57.3	
Sertraline	43.2	56.8	
Paroxetine CR	55.3	44.7	
Escitalopram	55.3*	44.7	
Distribution (%), LOT adjusted for therapy change <sup>†</sup>			
SSRI agent	180 days	<180 days	Therapy change
Fluoxetine	25.4	30.7	43.9
Paroxetine IR	24.8	36.9	38.3
Citalopram	25.5	34.2	40.3
Sertraline	28.1	36.9	35.0
Paroxetine CR	38.3	30.9	30.8
Escitalopram	37.7	30.5	31.8

\*Data for escitalopram were not available at time of analysis; therefore, rates were set equal to paroxetine CR.  
<sup>†</sup>LOT adjusted by assuming equal likelihood of therapy change regardless of achieving 180 days of therapy. For example, 43.9% of fluoxetine patients achieving 180 days were assumed to change therapy (43.9% x 45.4% = 19.9% of fluoxetine patients who achieve 180 days will have a therapy change; therefore, 25.4% of patients who achieve 180 days will not have a therapy change). A similar adjustment was made for <180 days.  
 SSRI indicates selective serotonin reuptake inhibitor; LOT, length of therapy; IR, immediate release; CR, controlled release.  
 Sources: References 4, 17.

**Table 3.** Resource Use/Cost Inputs

Resource	Model assumption/value (\$)
<b>Weighted average cost per prescription (wholesale acquisition cost)*</b>	
Fluoxetine	15.58
Paroxetine IR	64.23
Citalopram	32.74
Sertraline	68.96
Paroxetine CR	72.30
Escitalopram	59.13
<b>Average number of prescriptions filled per year</b>	
180 days	10.14
<180 days	3.81
Therapy change	12.30
<b>Average medical costs (\$)</b>	
180 days	4102
<180 days	5223
Therapy change	6741

\*Weighted average cost accounts for the distribution of the various strengths of each product, using wholesale acquisition costs for a 30-day prescription.

IR indicates immediate release; CR, controlled release.

Sources: References 18-20.

**Outcome Measures**

Based on the differential rates of length of therapy adjusted for therapy change for each SSRI agent shown in Table 2, patients are distributed into those who achieved at least 180 days of therapy, those who achieved less than 180 days of therapy, and those who had a therapy change. For example, in the hypothetical plan population of 32 096 patients taking SSRIs for anxiety, fluoxetine comprises 20.2% of the SSRI market, or approximately 6483 patients. Based on the literature, 25.4% of patients taking fluoxetine achieve 180 days of therapy (1647 patients), 30.7% achieve less than 180 days of therapy (1990 patients), and 43.9% have a therapy change (2846 patients).

After patients are distributed into the respective treatment cohort of at least 180 days of continuous therapy, less than 180 days of therapy, or therapy change for the open formulary policy and the GST formulary, resource utilization is calculated. Total medical costs inclusive of all claims for med-

ical-related services in a 1-year period and total annual antidepressant prescription costs for each formulary policy were estimated. A 1-year time frame was chosen to adequately capture differential costs in resource utilization after treatment. The total medical and pharmacy costs for each utilization pattern were determined, as well as the total medical and pharmacy costs. To compare costs across each formulary policy, a per member, per month (PMPM) cost was assessed for the GST policy versus the open formulary policy.

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**SENSITIVITY ANALYSIS**

A sensitivity analysis was conducted to measure how robust the results of the model were to changes in the base case model inputs and to determine what key inputs drive the model. Using a Monte Carlo simulation, the inputs were varied independently while holding all other variables constant, for a range of 20% around the mean base case input. This was repeated for 1000 trials to determine a range of cost estimates for each formulary model. A univariate sensitivity analysis was then performed around each variable to estimate the relative impact of changing the base case estimate. The distribution of all variables used in this model was assumed to be normal across a range of reasonable estimates.

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**RESULTS**

The simulation model represents the effects of implementing a GST formulary within a hypothetical health plan population of 1 million covered lives. The affected patients within the health plan consist of 5.9% of the entire population who are assumed to receive any antidepressant therapy, and 68% of these patients initiate antidepressant therapy with an SSRI agent.<sup>11</sup> This is approximately 4.0% of the total plan population, or 40 120 patients. As discussed above, the model assumes that of patients who receive antidepressant therapy, 80% are seeking treatment for anxiety-related illness, for a study population of 32 096 patients.

**Utilization Patterns**

As seen in **Figure 2**, therapy change was the most common utilization pattern observed (open formulary, 36.8%; GST formulary, 41.3%), and continuous therapy for longer than 6 months was the least common utilization pattern observed (open formulary, 29.8%; GST formulary, 25.3%). The GST formulary results in a higher number of patients requiring a therapy change or discontinuing therapy before 6 months and a lower number of patients who have continuous therapy for at least 6 months.

**Costs of Implementing a GST Formulary**

Due to the increase in therapy change rates, the total number of prescriptions filled during the 1-year period rises for the GST versus the open formulary (286 233 prescriptions annually for the GST formulary vs 282 904 prescriptions for the open formulary), but the total cost of SSRI therapy is lower for the GST (\$11.6 million for the GST formulary vs \$14.8 million for the open formulary) (**Figure 3**) due to decreased utilization of relatively higher-cost branded agents. The annual pharmacy costs of each formulary can also be represented by a PMPM cost of \$0.97 for the GST formulary and \$1.23 PMPM for the open formulary (a net reduction of \$0.26 PMPM for the GST formulary).

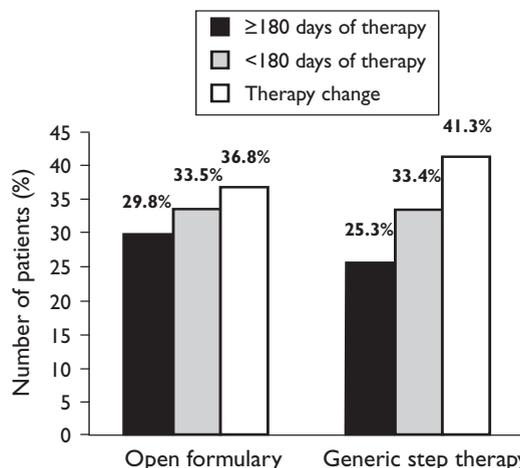
However, although the pharmacy costs associated with the GST formulary are lower, as expected, there is a significant increase in medical costs associated with implementing the GST formulary. Medical costs over a 1-year time frame totaled \$178.7 million for the GST formulary as compared with \$174.9 million for the open formulary. This can also be represented by a PMPM of \$14.89 for the GST formulary and \$14.57 for the open formulary, for a net increase of \$0.32 PMPM for the GST formulary. When combining medical and pharmacy expenditures over a 1-year time frame, the total cost associated with the open formulary is \$189.6 million compared with \$190.3 million associated with the GST formulary, for an additional cost of \$684 360, or \$0.06 PMPM for the total health plan population (**Figure 3**). Medical costs, which include hospitalizations, outpatient visits, and emergency department visits, constitute

between 92% and 94% of the total costs, with the remainder due to pharmacy costs.

**Sensitivity Analysis**

A univariate sensitivity analysis was conducted around each input to determine its relative impact on the model. Inputs were varied 20% around the mean of the base case scenario, with percentages truncated at 0% and 100% at each end when necessary. The results of the sensitivity analysis indicate that the model is most sensitive to changes in the weighted average cost of branded agents and the average annual medical costs for therapy change, and least sensitive to the incremental number of prescriptions filled per year (**Figure 4**). For the implementation of a GST to result in no net cost difference, assuming no changes in the level of discontinuation and therapy change, the weighted average cost of branded agents would have to increase to \$70.45 or the weighted average cost of generic agents would have to decrease to \$30.50. Only when the weighted average cost of branded agents was increased more than 20% over the base case value of \$65.81 and the weighted average cost of generic agents was decreased more than 20% from the base case value of \$34.01 did the implementation of a GST result in overall savings (net PMPM difference of -\$0.15 and -\$0.08, respectively).

**Figure 2.** Utilization Patterns in Patients With Anxiety Disorders



DISCUSSION

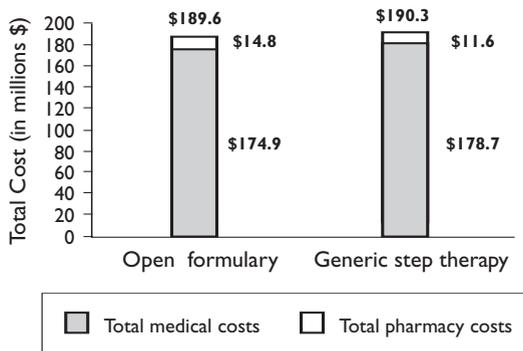
The results of the model indicate that implementing a GST formulary results in a reduction in pharmacy costs but an increase in medical costs, offsetting the savings from lower prescription prices for patients taking SSRIs for anxiety disorders or comorbid anxiety and depression. The findings of the model support previous work evaluating the cost implications of drug expenditures with a GST program. Motheral et al indicated that implementing a GST resulted in a reduction of \$0.29 PMPM for pharmacy costs, whereas the current model indicated a \$0.26 PMPM reduction.<sup>21</sup> However, the pharmacy cost reduction in the model was offset by an increase in medical expenditures of \$0.32 PMPM, providing a net cost increase to the health plan of \$0.06 PMPM rather than any overall cost savings.

Findings suggest that the higher medical expenditures may be an indirect result of an increase in the number of patients who fail to meet recommended therapy guidelines (ie, continuous therapy for at least 180 days) and an increased need for changes in SSRI therapy, such as a switch or augmentation, because of the restrictive formulary design. Similar findings of the negative impact of restrictive formularies were found in the literature. Streja et al found that patients in a health plan with a restrictive SSRI formulary were less likely to complete 180 days of continuous therapy (odds ratio, 0.20; *P* = .0004), with failure manifested

either as a failure to achieve 180 days of therapy or as noncontinuous therapy patterns, such as therapy switching.<sup>22</sup> This is of concern, because both patterns of utilization have been associated with an increased risk of relapse or recurrence of anxiety and/or depression.<sup>8,9,23</sup> As a result, more patients may have disease relapse or recurrence, driving utilization of both inpatient and outpatient medical services. For example, in a study evaluating more than 500 000 Medicare health maintenance organization patients, several trends were evident during a 2-year period after the implementation of a generic-only program: prescription drug expenditures decreased, antidepressant utilization likewise fell, but there was an increase in hospital admissions of approximately 3 additional hospitalizations per 1000 patients.<sup>24</sup> Similarly, Eaddy et al have demonstrated a clear and established relationship between length of antidepressant therapy and reductions in all-cause hospitalizations, with a 14% reduction in the likelihood of being hospitalized for every 30-day increase in length of therapy up to 90 days.<sup>25</sup>

It is apparent that the major premise behind a GST formulary is clinical equivalence across the SSRIs, so that selection of less expensive alternatives would result in similar clinical outcomes and lower prescription expenditures. However, all SSRIs are not clinically equivalent or equally tolerable in the treatment of anxiety disorders alone or with comorbid depression, and the restrictions on initiating a therapy with a demonstrated improved tolerability profile may increase the risk of relapse or recurrence, drive up medical resource utilization, and offset any pharmacy cost savings.<sup>5,10</sup> The model simulation demonstrates the cost implications of assuming equivalence across the SSRI class, as seen by the net cost increase to the health plan of \$0.06 PMPM after the implementation of a GST. In addition to the increased medical costs shown by the model, there are also associated administrative costs that were not captured. For instance, Motheral et al found that 24% of patients in a GST for SSRIs received a medical exemption for a branded agent after receiving the denial at

**Figure 3.** Total Pharmacy and Medical Costs (in Millions)



**Figure 4.** Impact of Varying Base Case Values on the PMPM Cost Difference of Implementing a GST Formulary

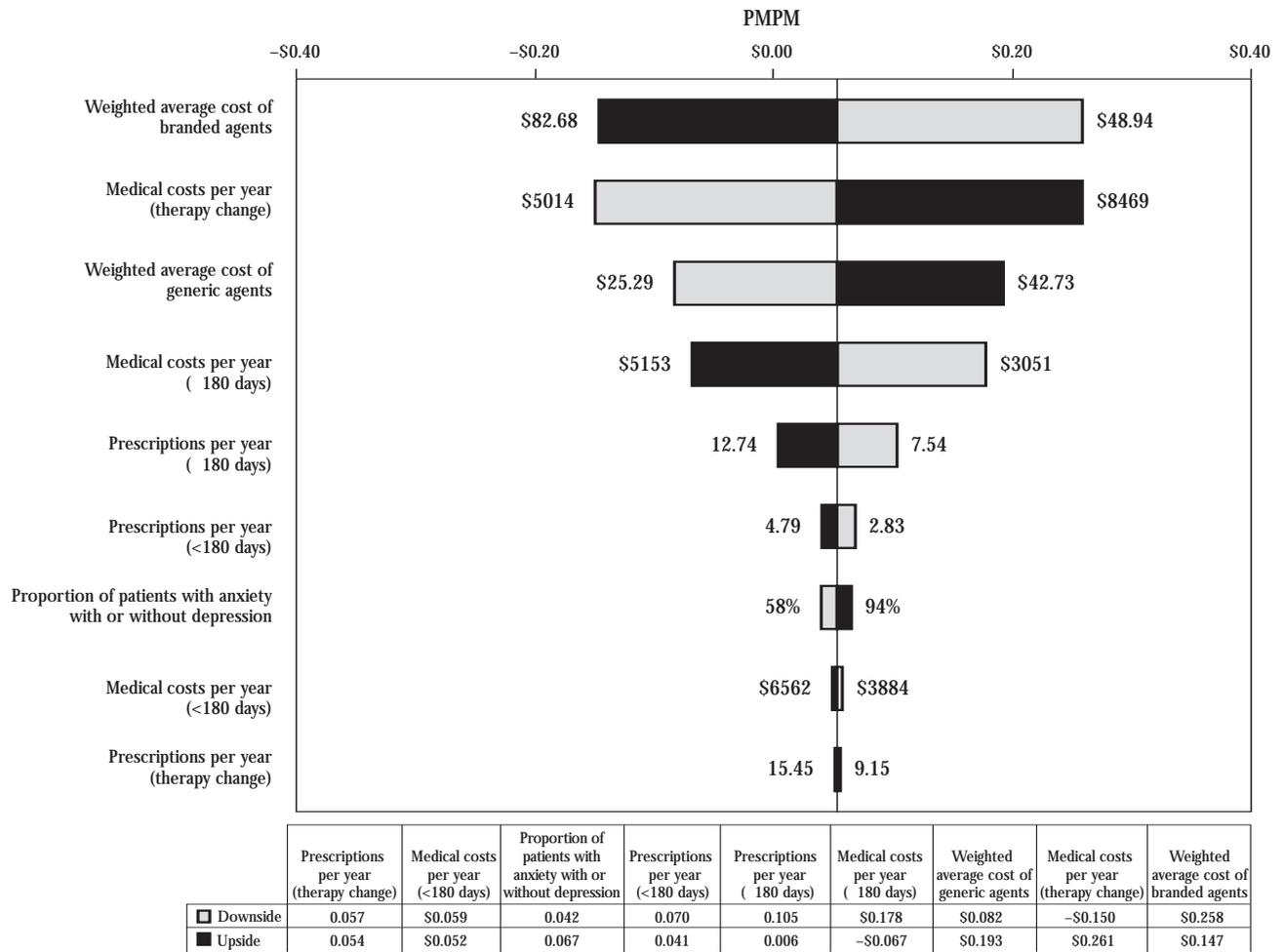


Figure 4 is a tornado diagram depicting the variables most influential to PMPM cost of implementing a GST formulary. Holding all other variables constant, each variable is varied around the base case value, between the ranges to the far left and far right of each bar. Based on this variance, the PMPM cost can be read from the x-axis; a positive PMPM represents an increased cost of implementing a GST formulary. The upside (solid) represents when the base case is increased, and the downside (gray) represents when the base case is decreased.

GST indicates generic step therapy; PMPM, per member, per month; 180 days, patients achieving continuous therapy for at least 180 days; <180 days, patients not achieving continuous therapy for at least 180 days.

the point-of-service.<sup>21</sup> This translates into even lower pharmacy cost savings for the health plan once the cost of the medical exemption process (typical cost of \$10-\$25 for each medical exemption) and the additional cost of the branded agents are factored in.<sup>21,26</sup>

Because the actual cost of a formulary decision to a health plan relies heavily on resource utilization, market makeup, and pricing, a sensitivity analysis was conducted

to identify the most critical factors that impacted the model results. The sensitivity analysis indicated that the differential PMPM cost between an open formulary and a GST formulary is most dependent on the current price of branded SSRI agents and least dependent on the cost difference between patients remaining on therapy for at least 180 days. Based on the model, and not factoring in administrative costs and member dissatisfaction, a decision maker may be

indifferent to a GST formulary if the price of all branded SSRI agents was \$70.45 while the price of generics was held constant at approximately \$34. However, this does not mean that SSRIs near or above this value negatively impact the cost savings with an open formulary system. For example, paroxetine CR is currently listed at \$72 but has the lowest discontinuation and therapy change rates of all of the SSRIs, which are the primary drivers for differences in medical costs.<sup>4,27</sup>

The methods and inputs used in estimating the impact of a GST formulary on a hypothetical health plan are subject to some important limitations. First, patterns of utilization (ie, length of therapy or therapy change) and cost of treatment were derived from published literature using health plan data and may not be applicable to all health plans depending on member characteristics. However, the results of the sensitivity analysis indicated that changes in resource utilization, such as yearly medical costs and the average number of prescriptions per year, had the least impact on the differential PMPM costs of a GST formulary. Additional naturalistic studies should be conducted to validate the results found here. The model assumed that 100% of all patients who receive an SSRI agent were being treated for either anxiety with or without depression (80%) or depression alone (20%) to simplify the model structure. However, it is understood that patients receive SSRI therapy for other indications such as migraines, although the exact figures are not known. This likely overestimates the economic impact of the GST. This variable also had a minimal impact on the results of the model, varying from an additional cost of the GST from \$0.04 to \$0.07 when the anxiety population decreased to 58% or increased to 94%, respectively.

Second, the model also assumed that there was 100% conversion from branded products to the generically available products within the health plan. Given various exemptions for branded products, this assumption may have resulted in an underestimation of the true costs of SSRI prescriptions.

Third, pharmacy costs reported may not accurately reflect health plan pharmacy

costs, as (1) prescription costs were derived from wholesale acquisition costs, which may not reflect health plan-specific discounting or rebating, and (2) patients who did not achieve 180 days of therapy were assumed to not resume therapy at a later date, which may understate pharmacy costs from gaps in therapy versus therapy discontinuation.

Finally, although the objective of this study was to evaluate the economic impact of a GST formulary, certain important variables were excluded, including administrative costs and any costs of implementation (such as patient or provider notification). The effects of the GST formulary on patient outcomes beyond prescription and medical resource utilization were not fully evaluated either, specifically the role of patient or provider satisfaction. For example, Cox et al reported that those patients who received a generic agent in place of the prescribed branded agent after implementation of a GST were significantly less satisfied with the subsequent generic agent.<sup>28</sup> Whether patient satisfaction with therapy influences therapy compliance has not been determined.

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**CONCLUSION**

As the number of antidepressants continues to grow in both new chemical entities and new generic formulations, it will be important for healthcare decision makers to fully understand differences in SSRI agents to create a clinically and economically sound drug benefit plan. The results of the model indicate that implementing a GST formulary may be associated with an increased number of patients who require a therapy change and who discontinue therapy early. These 2 patterns of utilization are associated with a higher risk of disease relapse or recurrence, suggesting a lower quality of care in this formulary plan. Based on current model inputs, a GST program would result in an increase of \$0.06 PMPM, which represents a \$0.32 PMPM increase in medical utilization and a \$0.26 PMPM decrease in pharmacy utilization. Further research is needed to evaluate the effects of a GST program in a real-world setting.

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