The Economic Impact of Introducing Serotonin-Noradrenaline Reuptake Inhibitors into the Brazilian National Drug Formulary

Cost-Effectiveness and Budget-Impact Analyses

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Abstract

Objective: To determine the cost effectiveness, from the Brazilian Ministry of Health viewpoint, of three antidepressant classes for major depressive disorder (MDD), and the budget impact of introducing serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs) into the current Brazilian national drug formulary, assuming a 6-month treatment duration.

Methods: An existing decision-tree model was adapted to Brazil, based on local guidelines. Clinical data were obtained from published meta-analyses. Patients included adults aged ≥18 years with MDD, diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, third and fourth editions (DSM-III/IV), with moderate-to-severe disease (Hamilton Depression Rating Scale [HAMD] ≥15 or Montgomery-Åsberg Depression Rating Scale [MADRS] ≥18), without co-morbidities or co-medications, receiving ≥6 weeks of treatment with SNRIs, selective serotonin reuptake inhibitors (SSRIs) and/or tricyclic antidepressants (TCAs). Clinical outcome was remission (HAMD ≤7 or MADRS ≤12). Direct costs (drugs, physician visits, hospitalisations) were included. Drug costs were obtained from the 2006 Brazilian National Drug Price List, and hospitalisation and physician costs from the 2006 Healthcare System database. Costs were valued in Brazilian Reais ($Brz), year 2006 values ($Brz1 = $US0.47). Univariate and Monte Carlo sensitivity analyses tested model robustness.

Results: Expected costs per patient treated were SNRIs $Brz4848; SSRIs $Brz5466; and TCAs $Brz5046, and overall success rates (primary plus secondary treatment across all decision tree branches) were SNRIs 78.1%; SSRIs 74.0%; and TCAs 76.4%. Average costs/success were SNRIs $Brz6209; SSRIs $Brz7385; and TCAs $Brz6602. SNRIs dominated in incremental cost-effectiveness analyses. Monte Carlo analysis confirmed drug classes' relative positions; however, there was considerable uncertainty. Introducing SNRIs into the formulary could generate average savings of 1% of the total budget, with a 52% probability of savings.

Conclusions: SNRIs appear to be cost effective against SSRIs and TCAs when prescribed to patients with MDD in Brazil. However, their inclusion into the national drug list would generate minor savings compared with the current formulary of SSRIs and TCAs. Thus, we considered such inclusion as 'cost-neutral', since no major probability of savings or increased expenditures were observed.

Depression, especially major depressive disorder (MDD), is a serious and pervasive disorder among adults worldwide, with an estimated lifetime prevalence of 10–25% among women and 5–12% among men.[1,2] A Brazilian study estimated that the lifetime prevalence of depression in Brazil was 2.8–10.2%.[3] Depressive symptoms are associated with decreased social functioning, poor health and high healthcare utilisation.[4,5] In the US, the estimated healthcare cost for treating depression in 2000 was $US83.1 billion.[6] Adjusted for inflation, that cost would have increased to about $US97 billion in 2006.

The choice of antidepressant has implications for safety and patient compliance, which may substantially affect costs.[6] This is especially true where the additional direct (i.e. acquisition) cost of a drug with a high rate of efficacy may reduce other direct and indirect costs related to the disease.[7]

Several pharmacological alternatives for depression are available throughout markets worldwide, including Brazil.[8] Currently, the three most prescribed classes of antidepressants are the serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs), the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants (TCAs). Significant differences in clinical efficacy and safety profiles have been found among these three pharmacological classes of antidepressants as well as within each of them.[9] Although prices of drugs from these pharmacological groups differ substantially, drug costs often represent only one-tenth of the total economic consequences of depression.[6]

Several health economic evaluations have been performed on antidepressants.[10] To date, studies have tended to involve economic evaluations of specific groups of interventions,[11,12] rather than the analysis of the full range of available interventions simultaneously.[10] Pharmacoeconomic analyses of SNRIs, SSRIs and TCAs have been described in the literature, and in all cases, these studies compared a single drug (i.e. venlafaxine) versus other antidepressant groups.[10]

Furthermore, in most cases, published pharmacoeconomic analyses have used 'clinical response' as the outcome, instead of the more stringent (and currently accepted standard) measure for clinical outcome, 'remission'.[13] In one study,[14] remission rates were used in the analysis, but only venlafaxine was used for the comparison to represent the drug class. None of the analyses to date has considered milnacipran (an SNRI) even though this drug has been available in many countries for a long time. Additionally, other newer agents (such as duloxetine and escitalopram) have been developed and marketed, but have not thus far been compared in economic analyses.[10] To date, no economic study of antidepressants has been performed in Brazil. A recent review of pharmacoeconomic analyses from South America found 24 full economic analyses published up to 2005, only one of which studied depression, specifically in Venezuela.[15]

In Brazil, a public-private managed healthcare system, drugs are financed differently depending on the type of health insurance. Private health maintenance organisations usually do not cover drugs or share their costs with patients. Individuals covered by the public-administered Single Healthcare System (Sistema Único de Saúde) have free access to all drugs listed in the National Essential Drug List (Relação Nacional de Medicamentos Essenciais; RENAME). The Brazilian National Drug Policy, set by the Ministry of Health, makes its decisions based on drug efficacy, safety, quality profile and drug price.[16] It does not currently use pharmacoeconom-

ic analysis as a tool for evaluating product registrations, reimbursement submissions or inclusions in the national drug formulary.[17,18] At present, the antidepressants included in RENAME are amitriptyline, clomipramine, fluoxetine and nortriptyline. As can be seen, three of the four drugs included in this formulary are TCAs, the remaining drug is an SSRI, and SNRIs are not included. Unfortunately, TCAs have a low tolerability profile,[9] which could lead to higher healthcare resource utilisation, and therefore higher overall costs in managing depression in Brazil. Thus, such information led us to postulate, what would be the economic impact of introducing SNRIs (in terms of cost effectiveness and budget impact) into the Brazilian National Drug Formulary?

The goal of this study was to perform a pharmacoeconomic analysis of three classes of antidepressants currently available in Brazil. Specifically, we aimed to identify the cost-effective drug class in Brazil for the treatment of MDD. We also sought to perform a budget impact analysis (BIA) to quantify what the economic impact of including SNRIs in the Brazilian national drug formulary would be.

Methods

Cost-Effectiveness Analysis

We performed a cost-effectiveness analysis of antidepressants for the management of MDD in Brazil. Patients were assumed to have MDD but no co-morbidities and were not receiving other medications. The analytic perspective was that of the Brazilian Government as a payer, and all direct costs of treatment were included. We examined three classes of antidepressants currently available on the Brazilian market.[8] The drugs included oral forms of SNRIs, SSRIs and TCAs given at therapeutic doses for ≥6 weeks of treatment.

The decision model used in this study was adapted from the 17-branch outpatient tree previously published by Einarson et al.[19] The choice of using a decision model for this pharmacoeconomic analysis of antidepressants in Brazil was based on the unavailability of clinical or naturalistic studies that would replicate clinical practice over a sufficient length of time. The time horizon was 6 months and two antidepressant drug regimens were included in the model (i.e. primary and secondary drug therapy). Since the data employed for building the original clinical decision model, for estimating its inputs, and validation was obtained using a Canadian expert panel,[19] we adapted the model for use in Brazil using the Brazilian Medical Association Guidelines for the Treatment of Depression.[20] However, we found that these guidelines followed the model very closely, and no modification of clinical pathways was necessary. Figure 1 shows a decision tree representing the pharmacoeconomic model.

We assumed that there was a 50/50 chance of patients being titrated or switched to a second therapy in the case of inadequate response to the primary treatment. Also, it was assumed that withdrawals due to adverse drug reactions (ADRs) occurred within the first 2 weeks of treatment, and that withdrawals due both to lack of efficacy and to clinical success (i.e. clinical remission) occurred after 4 weeks of treatment.[20] When patients were hospitalised (after second pharmacotherapy failed), they stayed for a period of 30 days,[21] and it was assumed that after this hospitalisation period patients would be in clinical remission. The 30-day hospitalisation period represents an average hospitalisation period of depressed patients described by the 2006 Brazilian public healthcare system database (DATASUS).[21] Following the hospitalisation period, treatment was continued with maximum daily doses of the second pharmacotherapy and weekly psychotherapy sessions, and adjunct lithium carbonate (300mg three times daily) was added to the pharmacological regimen.[20] Additionally, electroconvulsive therapy (ECT) was included in our model as a suggested approach to patients with MDD that did not respond to conventional treatment (pharmacological and psychological). Specifically, ECT was added to antidepressant treatment for all patients when both primary and secondary drug therapies failed, as suggested by the Brazilian clinical guidelines.[20]

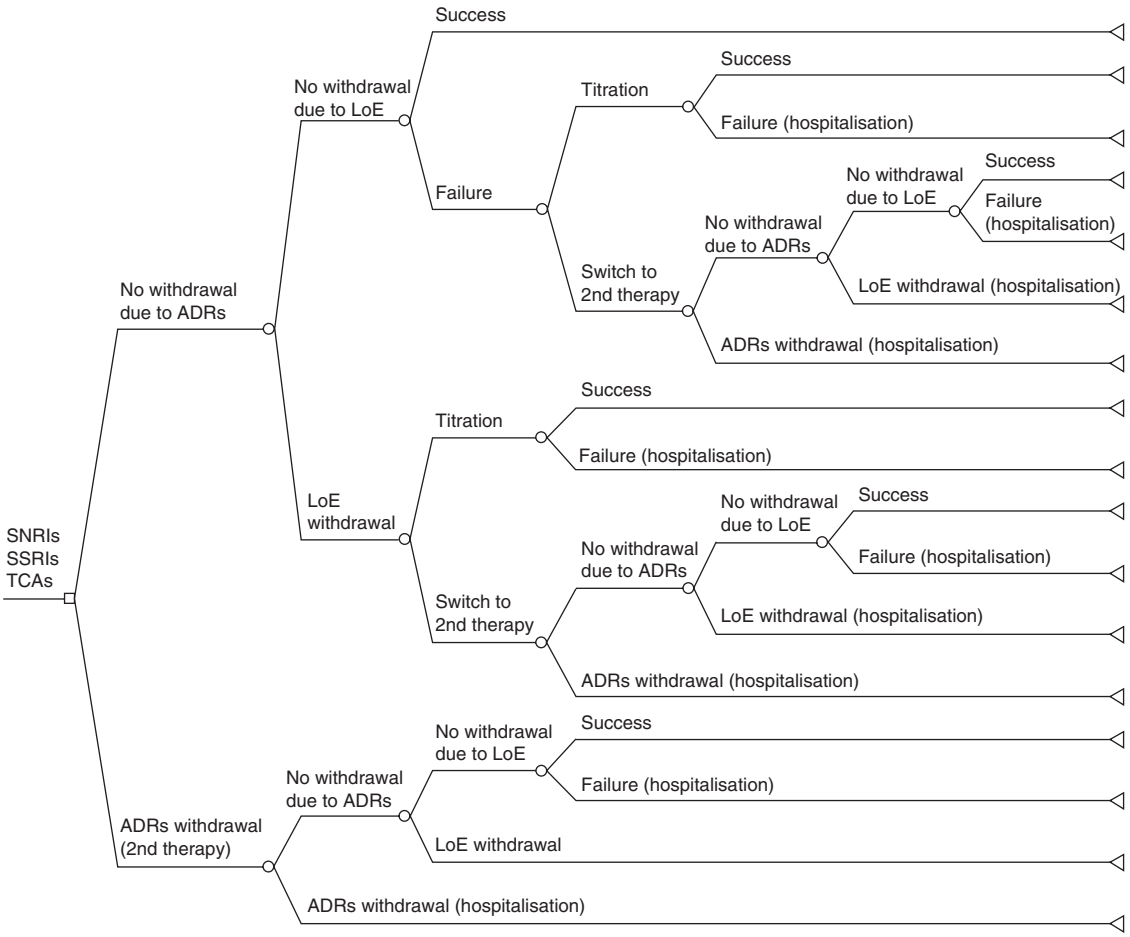

Fig. 1. Decision tree representing the pharmacoeconomic model for the management of major depressive disorder in Brazil. **ADRs** = adverse drug reactions; **LoE** = lack of efficacy; **SNRIs** = serotonin and noradrenaline (norepinephrine) reuptake inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

According to the Brazilian Clinical Guidelines for the Treatment of Depression,[20] patients should be followed-up for at least 4–6 weeks of initial treatment, and physician visits are advisable. In this model, every time a patient started a new therapy (primary or secondary) and no withdrawals were observed, they would make four physician visits and receive 4 weeks of drug therapy before a determination of success or failure would be made.[20] In the case of withdrawals due to ADRs, patients would receive 2 weeks of treatment and have two physician visits before switching to another drug. According to Machado et al.,[9] the most frequently reported ADRs by patients using antidepressants (e.g. dry mouth, nausea, dizziness, headache, sweating) are minor effects. Therefore, we did not incorporate costs due to ADRs, considering that the management of these ADRs would lead to minimal impact in the overall cost per patient treated.

SSRIs were used as secondary treatment for SNRIs and TCAs; TCAs were used as secondary treatment for SSRIs. The decision as to which secondary treatment would be used was based on both our clinical experience and clinical guidelines.[20] However, a rationale exists for the decisions presented. It is known that SSRIs have a good safety

profile, without an enhanced clinical efficacy (compared with SNRIs and TCAs).[9] The opposite is observed for TCAs.[9] Therefore, if we assume that a patient failed on SSRIs because of a lack of efficacy, the backup therapy would be a TCA. Additionally, if we assume that a patient would withdraw from TCA therapy because of an ADR, the backup therapy would be an SSRI. In the case of SNRIs, we used SSRIs as backup therapy as they are standard treatment in depression.

Clinical data were obtained from a recently published meta-analysis.[9] That study compared 15 head-to-head clinical trials involving at least two active treatment arms comparing antidepressant pharmacological therapy. Patients included in the meta-analysis were aged ≥18 years and diagnosed with MDD using any standard scale (e.g. DSM-III or higher version). Patients must have scored ≥18 on the Montgomery-Åsberg Depression Rating Scale (MADRS)[22] or ≥15 on any version of the Hamilton Depression Rating Scale (HAMD).[23]

The outcome of primary interest was remission, defined as a score of ≤7 on HAMD or of ≤12 on the MADRS scale measured ≥6 weeks after starting therapy. A secondary outcome was tolerability, which was defined in terms of withdrawals due to ADRs and lack of efficacy/effectiveness.

Since our cost-effectiveness analysis was conducted from the Brazilian government perspective, only direct costs were used. Drug costs were obtained from the 2006 Sanitary Vigilance National Agency (ANVISA) drug price list,[8] and were calculated using average costs for brand name products and generics, and assigned equal weights to all values within drug classes (i.e. assuming equal utilisation for all products). The prices contained in the ANVISA drug price list are negotiated by the Brazilian government for all payers, and for drugs placed on the formulary and for off-formulary drugs. Table I describes all drug costs and doses used in the analysis. Other resource utilisation costs (i.e. hospitalisations, physician visits, laboratory tests, psychotherapy, electroconvulsive sessions, etc.) were taken from the 2006 DATASUS,[21] and are described in table II. All analyses were performed using 2006 costs in Brazilian Reais ($Brz1 = $US0.47). Discounting was not performed, since the time horizon was <1 year.

Clinical remission rates and withdrawal rates were entered into the tree, then multiplied together to form a probability matrix. By multiplying the cumulative resource utilisation costs in each arm by the probability of the associated outcome for that arm and summing across all arms, we then estimated an overall weighted average (expected) cost for treatment with each drug. In addition, the probabilities from all arms terminating with success were combined to arrive at a total overall success rate for each drug. The expected cost per patient treated was then divided by the drug's success rate, to arrive at the expected cost per success (cost-effectiveness measure). Finally, an incremental cost-effectiveness analysis was performed for all drugs by sequentially calculating the incremental cost per success.

The 95% confidence limits for clinical rates from the meta-analysis[9] were then used as upper and lower limits for the sensitivity analyses. We performed a Monte Carlo analysis using 10 000 iterations, varying the inputs for remission rates and withdrawal rates (i.e. due to both ADRs and lack of efficacy) for both primary and secondary therapies. We also varied the costs of treatments across an assumed range of values using a pseudo-standard deviation of ±10%. For clinical variables, we used Normal distributions and for costs we used log-linear distributions in the Monte Carlo simulation, since costs most often display right skewness. Table III shows the variables used in the simulation with their respective standard deviations and distribution types. Other analyses included one-way sensitivity analysis for the assumption of 50/50 probability of titration or switching to a second therapy, in which the decision rate to switch therapy was increased to a maximum of 90% and then decreased to a minimum of 10%.

Budget-Impact Analysis

The BIA analysis was conducted from the Brazilian Ministry of Health perspective. The BIA was performed using a prevalence-based epidemiologi-

Table I. Drug costs (Brazilian Reais [$Brz], year 2006 values)[a,b] and doses (mg) of antidepressants utilised in the economic evaluation for Brazil[8]

Drug	Dose		Cost		
	DDD	MDD	per mg	per week (DDD)	per week (MDD)
SNRIs					
Duloxetine	40	60	0.11	29.87	44.80
Milnacipran	50	200	0.04	12.38	49.50
Venlafaxine	75	300	0.04	20.80	83.19
Overall cost			0.06	21.01	59.16
SSRIs					
Citalopram	20	80	0.10	14.27	57.09
Escitalopram	10	20	0.37	26.24	52.47
Fluoxetine	20	140	0.06	8.43	58.99
Paroxetine	20	70	0.09	13.18	46.12
Sertraline	50	250	0.03	12.21	61.07
Overall cost			0.13	14.87	55.15
TCAs					
Amitriptyline	150	300	0.01	12.42	24.83
Clomipramine	100	300	0.02	15.29	45.86
Imipramine	150	300	0.02	21.66	43.32
Nortriptyline	75	150	0.02	8.73	17.45
Overall cost			0.02	14.52	32.86

a $Brz1 = $US0.47.

b Overall costs represent a simple average cost across all comparators in the group.

DDD = defined daily dose; **MDD** = maximum daily dose; **SNRIs** = serotonin-noradrenaline (norepinephrine) reuptake inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

cal model with a time-horizon of 5 years, where 2006 was the base-case year. We utilised a Brazilian epidemiology study[3] that measured three population estimates. In that study, they calculated the proportions of patients diagnosed with MDD in three Brazilian cities. In order to use a single estimate for the overall population, we calculated a weighted average of the three estimates. This proportion was then multiplied by the estimated Brazilian population aged >18 years in 2006 and subsequent years and by the rate of patients covered by the Brazilian public healthcare system.[24] That calculation estimated the total number of patients eligible for pharmacological treatment each year. The number of patients estimated to receive a specific drug in each budget scenario was calculated by multiplying the market share rate of that drug by the estimated number of patients covered by the Ministry of Health who were eligible for pharmacological treatment in each year analysed in our time horizon.

Table II. Resource utilisation costs (Brazilian Reais [$Brz]; year 2006 values)[a] utilised in the economic evaluation[21]

Medical care	Cost
Hospital stay (per day, including all inpatient medical care costs)	625.40
Physician visit	7.55
Psychotherapy	2.55
Augmentation with lithium 300mg three times a day (per week)	9.22
Laboratory (initial regimen)	12.95
Lithium serum concentration	2.25
Electroconvulsive therapy (per session)	30.00

a $Brz1 = $US0.47.

The two scenarios used in our BIA were the current scenario in which only the two classes of antidepressants listed on the Brazilian National Formulary were used (i.e. TCAs and SSRIs) and a hypothetical drug formulary where SNRIs were introduced. In the hypothetical scenario, all three drug classes were listed. This decision was based on the clinical opinion that multiple therapeutic options

with different clinical patterns should be available in the national drug formulary for the management of MDD in Brazil. Market shares for drugs in these scenarios were based on a Canadian pharmacoepidemiological study of antidepressants,[25] since no such Brazilian or Latin American studies were found.

The impact on two separate budgets was determined. The first analysis included only drug acquisition costs to examine affordability issues and the direct impact on the drug budget alone. The economic impact was calculated by multiplying the estimated number of patients eligible during the current year by the drug acquisition cost for the amount used over the 6-month treatment period. The second analysis included drug costs plus all of the relevant costs associated with the consequences of drug use and the management of depression (i.e. hospitalisations, physician visits, etc.) to estimate the total Ministry budget impact. The economic impact of the second analysis was measured by multiplying the expected cost per patient treated from the 6-month cost-effectiveness model by the estimated number of eligible patients during the current year. Finally, we subtracted the total cost estimated in the current scenario from the total cost estimated for the hypothetical cost-effective scenario to arrive at a budget impact for the 6-month treatment time horizon. The discount rate was 5% per year.

Sensitivity analysis was performed using Monte Carlo simulation with 10 000 iterations. Variations in the overall cost of treatment (i.e. expected cost per patient treated) for each drug included in both the current and the hypothetical cost-effective drug scenarios were analysed. For all drugs included in the BIA, we used log-linear distributions and the resulting 95% confidence interval (CI) of the expected cost per patient treated, previously calculated in the Monte Carlo simulation of the cost-effectiveness analysis for lower and upper limit variations. Data were presented as best- and worst-case scenarios for the total budget impact. Additionally, the probability of savings (i.e. percentage of simulations that produced savings) by using SNRIs was also calculated.

Results

Cost-Effectiveness Analysis

By pharmacological class, the expected costs per patient treated were SNRIs $Brz4848; SSRIs $Brz5466; and TCAs $Brz5046. Overall success rates (primary + secondary treatment across all decision tree branches) for the three pharmacological classes were SNRIs 78.1%; SSRIs 74.0%; and TCAs 76.4%. Average costs per success were SNRIs $Brz6209; SSRIs $Brz7385; and TCAs $Brz6602.

However, the true pharmacoeconomic results lie in the incremental cost-effectiveness ratios. When an incremental cost-effectiveness analysis was performed, by pharmacological group, SNRIs were dominant (i.e. they had the highest overall rate of efficacy along with the lowest expected cost per patient treated). In quantitative terms, SNRIs gener-

Table III. Variables used in the Monte Carlo simulation, with their respective distributions and standard deviations (SD)

Drug class	Clinical rates per person treated[a,b]			Costs[c] per week per person treated[d]	
	remission (SD)	LoE withdrawals (SD)	ADR withdrawals (SD)	DDD (SD)	MDD (SD)
SNRIs	0.635 (0.054)	0.062 (0.017)	0.103 (0.020)	21.01 (2.10)	59.16 (5.92)
SSRIs	0.543 (0.068)	0.072 (0.020)	0.083 (0.019)	14.87 (1.49)	55.15 (5.51)
TCAs	0.689 (0.072)	0.099 (0.036)	0.198 (0.032)	14.52 (1.45)	32.86 (3.29)

a Normal distribution.

b Clinical rates were obtained from Machado et al.[9]

c Costs are presented as Brazilian Reais ($Brz); year 2006 values; $Brz1 = $US0.47.

d Log-linear distribution.

ADRs = adverse drug reactions; **DDD** = defined daily dose; **LoE** = lack of efficacy; **MDD** = maximum daily dose; **SNRIs** = serotonin-noradrenaline (norepinephrine) reuptake inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

Table IV. Overall results[a] from the pharmacoeconomic analysis of antidepressants in Brazil

Drug class	Resource utilisation costs per patient treated				Overall (expected) costs per patient treated	Expected success rates	Cost per success	Cost effectiveness
	hospitalisation	physician visit	drugs[b]	other[c]				
SNRIs	4112	49	678	10	4848	0.781	6209	Dominant[d]
SSRIs	4875	52	525	14	5466	0.740	7385	Dominated
TCAs	4420	49	565	12	5046	0.764	6602	Dominated

a Costs are presented as Brazilian Reais ($Brz), year 2006 values; $Brz1 = $US0.47.

b Drug costs include both primary and secondary therapies and augmentation with lithium.

c 'Other' resource utilisation costs include laboratory tests, electroconvulsive therapy and psychotherapy.

d Based on an incremental cost-effectiveness analysis.

SNRIs = serotonin-noradrenaline (norepinephrine) reuptake inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

ated savings of $Brz198 per patient treated and 1.6% of extra effectiveness compared with the drug having the next lowest cost-effectiveness ratio (TCAs). A 10% difference in effectiveness would be considered clinically important.[9] Table IV presents treatment costs, clinical efficacy and cost-effectiveness ratios for all studied drugs.

Results from the Monte Carlo simulation for the cost-effectiveness analysis are presented in table V. They are similar to the original findings of the cost-effectiveness analysis.

The resulting probabilities of SNRIs to generate a lower cost per patient treated compared with SSRIs and TCAs were 74.8% and 58.5%, respectively. Break-even analysis (increasing/decreasing clinical inputs from the model until cost-effectiveness equality of all three classes of antidepressants was achieved) showed that our pharmacoeconomic results were sensitive to antidepressant clinical efficacy. To produce cost-effectiveness ratios equal to those of SNRIs, the remission rate of SSRIs would have to increase by 9.6% (from 54.3% to 63.9%) and TCAs by 2.0% (from 68.9% to 70.9%). Both of those increased remission rates (i.e. 63.9% and 70.9%) lie within their 95% CIs, respectively, as reported in the meta-analysis by Machado et al.,[9] indicating sensitivity. Similarly, the remission rate of SNRIs would have to decrease from 63.5% to 57.6% to produce a ratio equal to that of SSRIs and to 61.9% to be equal to TCAs. These values also lie within their 95% CI.

Table V. Results from the Monte Carlo simulation examining the sensitivity of the cost-effectiveness analysis[a]

Drug class	Mean cost per patient treated (SD)	95% Confidence intervals	
		LL	UL
SNRIs	4886 (800)	3318	6454
SSRIs	5498 (1029)	3480	7515
TCAs	5068 (898)	3307	6830

a Costs are presented as Brazilian Reais ($Brz), year 2006 values; $Brz1 = $US0.47.

LL = lower limit; **SD** = standard deviation; **SNRIs** = serotonin-noradrenaline (norepinephrine) reuptake inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants; **UL** = upper limit.

Budget-Impact Analysis

The estimated weighted average prevalence of depression in Brazil was 3.52%. This rate, when multiplied by the Brazilian population >18 years of age (117.9 million people in 2006) resulted in an estimated 4.2 million Brazilians with MDD in 2006. However, our study was conducted from the perspective of the Brazilian Ministry of Health, which covers approximately 46% of the population (i.e. through the public healthcare system share). Therefore, the total expected number of patients with depression covered by the public healthcare system would be 1.9 million people in 2006, assuming patients with depression are evenly distributed throughout the public and private sectors.

The epidemiologically based model assumed two types of scenarios. In the first, the two drug classes listed on the Brazilian national drug formulary (i.e. SSRIs and TCAs) each had 50% market share.[25] Thus, each listed drug class would be prescribed to an estimated 954 612 patients. In the hypothetical scenario where SNRIs were included in the National

Drug Formulary, the proportions of the prescription market were 25% for SNRIs and TCAs, and 50% for SSRIs.[25] Thus, the estimated number of patients receiving SNRIs and TCAs would be 485 947, and 941 396 patients would be receiving SSRIs.

Under the current scenario, it was estimated that $Brz673.3 million would be spent on the two antidepressant classes listed in the current national drug formulary in 2006. Under the hypothetical scenario using the three antidepressant classes, the estimated cost to the Brazilian Ministry of Health in 2006 was $Brz747.6 million. The budget impact, with respect to the increased acquisition costs of the newer drugs, would be an increased expenditure of $Brz74.4 million (11.0%) in 2006 for 6 months' drug therapy in the management of depression.

When we analysed the total healthcare budget, the current drug formulary scenario was associated with a total healthcare cost of $Brz10.0 billion in 2006, whereas in the hypothetical expanded scenario, the estimated cost for all healthcare was $Brz9.9 billion. The budget impact in this case would be a saving to the healthcare system of $Brz94.5 (1.0%) million for a 6-month period in 2006.

Table VI shows the overall results for the BIA from 2006 to 2010. In the total time horizon, $Brz491.5 million could be saved by using SNRIs. The worst-case scenario generates additional yearly expenditures of $Brz3.3 billion and the best-case scenario generates yearly savings of $Brz3.5 billion by using SNRIs. Both base- and worst-case scenarios are represented by the lower and upper limit of the 95% CI of the average budget impact, respectively. Results from the Monte Carlo simulation suggest that, on average, the probability of savings by including SNRIs was 52.4% per year.

Discussion

This pharmacoeconomic analysis suggests that SNRIs may be cost effective compared with TCAs and SSRIs for the treatment of depression within the Brazilian healthcare context. These findings were supported by the Monte Carlo simulation, where

Table VI. Budget-impact analysis[a] considering drug acquisition costs and total healthcare costs[b] for the treatment of major depression in Brazil

Parameter	2006	2007	2008	2009	2010
Epidemiology					
Population age ≥18 years[24]	117 911 593	120 371 138	122 779 682	125 139 869	127 407 728
Prevalence of depression (%)[3]	3.52	3.52	3.52	3.52	3.52
Number of depressed patients	4 150 488	4 237 064	4 321 845	4 404 923	4 484 752
Rate of patients covered by the public healthcare system (%)[24]	46	46	46	46	46
Number of depressed patients covered by the public healthcare system	1 909 225	1 949 049	1 988 049	2 026 265	2 062 986
Budget impact ($Brz)					
Drug acquisition costs					
Current drug formulary	673.3	654.6	635.9	617.3	598.5
Hypothetical formulary	747.6	726.9	706.1	685.4	664.6
Impact[c]	**74.4**	**72.3**	**70.2**	**68.1**	**66.1**
Total costs[b]					
Current drug formulary	10 035.4	9756.9	9478.2	9200.4	98921.1
Hypothetical formulary	9940.9	9665.1	9339.0	9113.8	8837.1
Impact[c]	**−94.5**	**−91.8**	**−89.2**	**−86.6**	**−84.0**

a Costs are presented in million Brazilian Reais ($Brz), year 2006 values; $Brz1 = $US0.47. All costs were discounted at 5% per annum.

b Total costs included drug treatment costs, physician visits costs, hospitalisation costs, etc.

c Positive values indicate increased costs and negative values indicate savings.

cost-effectiveness ratios maintained their relative positions, with SNRIs remaining the least costly, then TCAs, and SSRIs being the most costly. However, the overall result from our uncertainty analysis showed that the CIs of the average cost per patient treated of most of the drugs are relatively similar, and overlap substantially. This result was attributed to variation of the remission rates included in the model (data presented in table III). In other words, our cost-effectiveness hierarchy of antidepressants in Brazil is sensitive to the clinical outcomes evaluated here (i.e. clinical remission and withdrawals). Additionally, in probabilistic terms, the probabilities of SNRIs to generate lower costs per patient successfully treated compared with SSRIs and TCAs were considered small. Therefore, there is a realistic chance of the treatment groups being equally effective.

The one-way sensitivity analysis (data not shown) changing the probability of titration or switch to second therapy did not change our overall hierarchy of findings for cost per patient successfully treated. The decisions of whether to switch to another drug or to titrate increased or decreased the average cost per patient successfully treated for some drugs. Generally, the choice of titration reduced the expected cost per patient successfully treated by not adding other drug therapy and other resource utilisations to patients' treatment. In clinical practice, the choice of whether to switch or titrate should be taken carefully and ethically, where the patient's clinical characteristics (e.g. drug tolerance, depressive symptoms remission) should be the main focus for decisions, regardless of the economic outcomes.

To our knowledge, no other pharmacoeconomic evaluation of antidepressants in Brazil has been performed and published in the literature. Pharmacoeconomic analyses[15] from other countries comparing SNRIs, SSRIs and TCAs can be found in the literature, but they are all different from our study. Almost all other analyses have used clinical response as the outcome of interest; however, we have used clinical remission, which we believe is to be preferred. The studies[10] that did use remission as their outcome all compared other drugs or drug classes versus venlafaxine as the sole representative of the SNRIs. We have also included all of the available SNRIs, such as milnacipran and duloxetine.

Our cost-effectiveness analysis matches with other published economic results that compared the same three pharmacological classes of antidepressants. We all found that SNRIs were generally cost effective compared with SSRIs or TCAs,[14,19] and a cost-effective hierarchy has been observed. In the Brazilian national drug formulary, 75% of its antidepressant choices are TCAs. Using drugs from this class is likely to cause unnecessary resource consumption due to their adverse toxicity profile, which will subsequently result in an increase in overall healthcare expenditures to the Brazilian Ministry of Health. This suggestion was somewhat confirmed by our BIA.

We estimated that on average, approximately $Brz100 million (≈$US50 million) could be saved each year by the Brazilian Ministry of Health for a 6-month management of depression, by including SNRIs in the National Drug Formulary. However, this base-case scenario is considered to be 'cost-neutral', since our uncertainty simulation for the BIA estimated that only 52% of the simulations generated savings by including SNRIs in the current drugs listed in the Brazilian National Drug Formulary. Additionally, the estimated best- and worst-case scenarios are numerically very similar, where no explicit savings or expenditures were observed.

On average, the estimated drug budget would increase by 10% by including SNRIs in the Brazilian National Drug Formulary. However, the reduction in healthcare resource utilisation (mostly in hospitalisations and physician visits) leads to a small, but positive, total budget impact (i.e. savings of 1% in the total budget). These reductions in healthcare use are attributed to the higher remission rates of SNRIs (i.e. higher remission rates) employed in our analysis.[9] This led us to estimate that a small proportion (0.41%) of additional patients would be successfully treated each year from the inclusion of SNRIs in the drug formulary. Further-

more, although not included in our analysis, these additional successfully treated patients could give rise to substantial societal savings by reducing the number leisure days lost, absences from work, etc.

Our study has several model limitations. The model adaptation used information from local clinical guidelines[20] instead of using clinical experts. In this case, we assumed that all pertinent information regarding major depression management was evidence-based and included in the referenced guidelines. Clinical data were taken from worldwide studies and not local studies, and thus we used efficacy data instead of effectiveness data. In this case, our model tried to mimic real-life practice by including withdrawals first. Moreover, the results presented here were generalised by drug class. The pharmacoeconomic impact of individual antidepressants on the Brazilian Ministry of Health budget could be different and should be investigated in future research.

Also, a 6-month time horizon was chosen to reflect 'best practice' for pharmacological treatment of a first depressive episode. Eventually, the clinical management of depression may be longer and additional months or years of drug therapy are required.[26] However, the benefit of pharmacological treatment beyond 6 months has only been demonstrated for groups with historical recurrent depressive episodes.[27]

Our CEA and BIA were limited to the acute phase of treatment (i.e. the first 6 months). We did not incorporate costs for patients whose depression had relapsed or recurred after 6 months. As well, many patients would be given treatment for longer periods of time. That would add to the impact on the drug budget. We estimated that, if these patients were treated for a further 6 months (until the end of the year), they would essentially double the drug impact on the budget (from $Brz74.4 million [table VI] to $Brz148.8 million). At the same time, the overall healthcare savings would decrease from $Brz94.5 million to $Brz20.1 million in the first year. Comparable results would be produced in subsequent years.

Additionally, market shares for drugs in the evaluated budget analyses were obtained from other countries. It is known that different rates of prescribing and/or adoption of new and old drugs exist from one country to another, and therefore variations would be expected in the estimated budget impacts.

Finally, we did not account for treatment adherence in our model. Reliable data regarding antidepressant adherence were not found. However, we acknowledge that different patterns for drug adherence exist, and could have a substantial impact in the overall clinical effect and costs, since some drugs compared here are administered once daily and others twice or more daily.

Conclusions

Our pharmacoeconomic analysis suggests that, from the Brazilian healthcare perspective, it is unlikely that there are significant differences in cost effectiveness between SNRIs, SSRIs and TCAs.

The addition of SNRIs to the Brazilian National Drug Formulary could, on average, generate savings of approximately $Brz100 million per annum, compared with the current drug formulary (TCAs and SSRIs). However, we considered such inclusion as 'cost-neutral', since there was considerable uncertainty surrounding this estimate. Future research should evaluate the opportunity and possible benefits of using pharmacoeconomic evaluations in Brazil to inform the selection of drugs for the country's drug formulary or market entry. Additionally, the impact on the Brazilian Ministry of Health budget of any changes should be assessed.

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References

1. Diagnostic and statistical manual of mental disorders IV-R. 4th ed. Washington, DC: American Psychiatric Association, 2000

2. Moore JD, Bona JR. Depression and dysthymia. Med Clin North Am 2001; 85 (3): 631-44
3. Almeida-Filho N, Mari JDJ, Coutinho E, et al. Brazilian multicentric study of psychiatric morbidity: methodological features and prevalence estimates. Br J Psychiatry 1997; 171: 524-9
4. Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. JAMA 1992; 267: 1478-83
5. Hoeper EW, Nycz GR, Regier DA, et al. Diagnosis of mental disorder in adults and increased use of health services in four outpatient settings. Am J Psychiatry 1980; 137: 207-10
6. Greenberg PE, Kessler RC, Birnbaun HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry 2003; 64: 1465-75
7. Montgomery S, Doyle JJ, Stern L, et al. Economic considerations in the prescribing of third-generation antidepressants. Pharmacoeconomics 2005; 23: 477-91
8. Ministério da Saúde. Agencia Nacional de Vigilancia Sanitária – ANVISA. Lista de preços de medicamentos [online]. Available from URL: http://www.anvisa.gov.br [Accessed 2006 Apr 6]
9. Machado M, Iskedjian M, Ruiz I, et al. Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. Curr Med Res Opin 2006; 22: 1825-37
10. Barrett B, Byford S, Knapp M. Evidence of cost-effective treatments for depression: a systematic review. J Affect Disord 2005; 84: 1-13
11. Byford S, Bower P. Cost-effectiveness of cognitive-behavioural therapy for depression: current evidence and future research priorities. Expert Rev Pharmacoecon Outcomes Res 2002; 2: 457-64
12. Hylan TR, Buesching DP, Tollefson GD. Health economic evaluations of antidepressants: a review. Depress Anxiety 1998; 7: 53-64
13. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991; 48: 851-5
14. Lenox-Smith A, Conway P, Knight C. Cost effectiveness of representatives of three classes of antidepressants used in major depression in the UK. Pharmacoeconomics 2004; 22: 311-9
15. Machado M, Iskedjian M, Einarson TR. Quality assessment of published health economic analyses from South America. Ann Pharmacother 2006; 40: 943-9
16. Ministério da Saúde. Agência Nacional de Vigilância Sanitária – ANVISA. Legislação em Vigilância Sanitária. Portaria Nº 1.587, de 3 de setembro de 2002 [online]. Available from URL: http://www.anvisa.gov.br [Accessed 2006 Apr 4]
17. Mota DM, Fernandes MEP, Coelho HLL. Farmacoeconomia: um instrumento de eficiência para a política de medicamentos do Brasil. Acta Farm Bonaerense 2002; 22: 177-86
18. Ministério da Saúde. Agência Nacional de Vigilância Sanitária – ANVISA. Legislação em Vigilância Sanitária. Portaria Nº 3916, de 30 de outubro de 1998 [online]. Available from URL: http://www.anvisa.gov.br [Accessed 2006 Apr 4]
19. Einarson TR, Addis A, Iskedjian M. Pharmacoeconomic analysis of venlafaxine in the treatment of major depressive disorder. Pharmacoeconomics 1997; 12: 286-96
20. Fleck MPA, Lafer B, Sougey EB, et al. Guidelines of the Brazilian Medical Association for the treatment of depression (complete version). Rev Bras Psiquiatr 2003; 25: 114-22
21. Ministério da Saúde. Sistema Único de Saúde – DATASUS [online]. Available from URL: http://www.saude.gov.br [Accessed 2006 Apr 10]
22. Montgomery SA, Åsberg M. A new depression scale designed to be more sensitive to change. Br J Psychiatry 1979; 43: 382-9
23. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56-62
24. World Health Organization (WHO) [online]. Available from URL: http://www.who.int/countries/bra/en [Accessed 2006 Apr 10]
25. Hemels ME, Koren G, Einarson TR. Increased use of antidepressants in Canada: 1981-2000. Ann Pharmacother 2002; 36: 1375-9
26. Kupfer DJ. Long-term treatment of depression. J Clin Psychiatry 1991; 52: 28-34
27. Anderson IM, Nutt DJ, Deakin JF. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. J Psychopharmacol 2000; 14: 3-20

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