ARTIGO ORIGINAL
ORIGINAL ARTICLE

Economic assessment of major depressive disorder treatment using different therapeutic classes at ISSSTE

Jocelyn Ramírez[1], Héctor Dueñas[1], Rosa-María Galindo[2]

Keywords:
economic assessment, depression, Mexico

SUMMARY

Objective: The objective of the present study was to determine the cost-effectiveness associated with three therapeutic classes for treating major depressive disorder (MDD) from the public healthcare payer perspective in Mexico. **Methodology:** To evaluate health and cost outcomes, a previously published decision model was adapted in order to reflect the usual MDD treatment practice at the Institute for Social Security and Services for State Workers in Mexico (ISSSTE) during a 3-months time horizon. The three therapeutic classes included in the present analysis were: Selective Serotonin Reuptake Inhibitors (SSRI), Tricyclic Antidepressants (TCA) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI). Only direct medical costs were considered either generic drugs or brand-name antidepressants with patent protection were analyzed. All costs are expressed in 2010 US dollars (Exchange Rate 1 US: 12.50 MXN pesos). **Results:** Within the three therapeutic classes assessed, expected value for one patient with each three options was distributed as follows: $5,001; $4,215; $4,078 for SSRI, TCA, and SNRI, respectively. The alternative with a greater expected remission rate was the SNRI class. For every thousand patients treated with SNRI, TCA, and SSRI, 725, 718, and 665 patients are expected to achieve remission, respectively. For every thousand patients treated with SNRI instead of TCA, there will be $ 68,272 cost savings over a period of 3 months. Likewise, when compared with SSRI, savings generated by SNRI are more than $ 367,437 for every thousand treated patients. **Conclusion:** The results of the present analysis suggest that SNRI as a therapeutic class in the treatment of MDD represent a dominant strategy.

Introduction

Evidence shows that depression is among the most common health-related conditions that increase lost productivity costs (McCunney RJ, 2001; Fautrel B & Guillemin F, 2001; Riedel JE, 2002; Berndt ER *et al*, 2000; Greenberg PE *et al*, 1993; Simon GE *et al*, 2000; Simon GE *et al*, 2001), mainly due to its high prevalence and associated comorbidities. Although workers with depression show up at work, their productivity is substantially decreased by this condition (Stewart WF *et al*, 2003).

Prevalence of depression

The diagnosis of major depressive disorder (MDD) is based on the presence of depression and anhedonia during the same two-week period, and the presence of any of the following five symptoms most of the day: (i) depression; (ii) pronounced decrease of interest or pleasure in activities; (iii) significant weight loss or weight gain, without a diet ; (iv) insomnia or hypersomnia; (v) restlessness/psychomotor retardation; (vi) fatigue or loss of energy; (vii) low or excessive self-esteem, or inappropriate guilt (viii) slowed thinking or decreased concentration; and (ix) frequent thoughts of death, dying or suicide (American Psychiatric Association, 2000). Clinical recognition of the disease is frequently complicated by the need to take the specific time to recognize it, and by the frequent physical symptoms, especially pain, in the presentation of depression (Muñoz R *et al*, 2005). Major Depressive Disorder is a frequent disease at all levels of the healthcare system.

Major depressive disorder is a psychiatric condition associated to psychological, behavioral, physical symptoms and a significant comorbidity, affecting 340 million people worldwide (Greden GF, 2003). According to the National Psychiatric Epidemiology Survey 2003, 9.1% of the overall Mexican population experiences an Affective Disorder at least once in

Received on: 19/07/2011 **Approved for publication on:** 07/11/2011

1. Eli Lilly and Company Mexico, S.A. de C.V., 2. At the time the study, the author worked at Eli Lilly and Company Mexico

Institution where the study was developed: ISSSTE Institute for Social Security and Services for State Workers in Mexico

Financing: this study was sponsored by Eli Lilly de Mexico S.A de C.V

Corresponding author: Jocelyn Ramírez - Barranca del Muerto 329. 1st Floor, Col. B. Juarez. Mexico City, DF, Zip Code 03900

their lifetime; Depressive Disorder represented 5.7% of these cases (Medina-Mora ME *et al*, 2003).

Impact of depression on health

The World Health Organization (WHO) defines Major Depressive Disorder as a chronic disease for reasons such as: high rate of relapse and recurrence (Salomon DA *et al*, 2000), frequent phenomenon due to different circumstances related to therapeutic compliance, as well as frequent residual symptoms occurring despite of therapy with Selective Serotonin Reuptake Inhibitors (SSRI) (Greco T el al, 2004; Thase ME *et al*, 1992; Judd LL *et al*, 2000). Chronicity in depression involves important disturbances in the quality of life of patients and their relatives, their productivity and school performance (Miller IW, 1998), and is directly related to increased use of alcohol, drug abuse and greater use of institutional and private health services (Ronald C *et al*, 2003). In addition, an increase in morbidity and mortality has been shown in different MDD related diseases: strokes (Everson SA *et al*, 1998), myocardial infarction (Frasure-Smith N, 1993), diabetes and AIDS (Lustman PJ *et al*, 2000; De Groot M *et al*, 2001; Ickovics JR *et al*, 2001).

Depression treatment

The efficacy rate reported by the largest practical trial conducted to date, STAR-D (Sequenced Treatment Alternatives for Depression), is 30% for citalopram (40 mg daily), which represents the prototype of Selective Serotonin Reuptake Inhibitors (SSRI), the efficacy rate that can be expected in regular practice conditions with this therapeutic class (Trivadi *et al*, 2006).

Evidence suggests that efficacy rates of selective serotonin and norepinephrine reuptake inhibitors (SNRI) are higher than antidepressants that act on one single neurotransmission circuit (Thase ME *et al*, 2001; Tran P *et al*, 2003; Machado M & Einarson TR, 2010). Thus, it is important to establish the cost-effectiveness relationship of these drugs in order to measure what this difference in efficacy rates means for the healthcare system.

According to the World Health Organization (WHO) depression is related, to a large extent, to the burden associated with nonfatal, negative health results (World Health Organization). In 2000, depressive disorders were estimated to affect more women (4930 in 10,000) than men (3199 in 100,000), representing the fourth cause of disease burden in women, and the seventh in men, worldwide (Ustün TB *et al*, 2004). Finally, MDD is one of the causes that generates a greater number of life years lost due to disability (World Health Organization, 2005).

A great part of literature has documented that depression represents a substantial burden to society (Zeiss AM & Lewinsohn PM, 1988; Broadhead WE *et al*, 1990; Rhode P et. al, 1990). One of the most recent documents evaluating total costs associated with MDD estimates that the annual costs per patient (2005 values, in US $) were significantly lower in stable patients (US$ 6,215) than in intermediate patients (US$ 7,317) and unstable patients (US$ 9,948; p>0.001) (Birnbaum HG *et al*, 2009).

For all these reasons, the decision process involving antidepressants therapy is very important in the Mexican healthcare system since the first prescription decision should consider the evidence of efficacy; and direct and indirect costs of treatment related to consequences of the relapse cycle of depression.

A recent meta-analysis (Machado M *et al*, 2007a) assessed different classes of antidepressants, SSRI, SNRI and tricyclic antidepressants (TCA), considering the results of 15 head-to-head, randomized studies with 2,458 patients. Remission was considered the primary efficacy measurement, and was determined by a score ≤ 7 in the Hamilton Rating Scale for Depression (HAMD), or ≤ 12 in the Montgomery-Asberg Depression Rating Scale (MADRS). Results showed that SNRI are placed as a strategy with the best remission rates (statistically significant both for outpatient and inpatient management) with 49%; followed by TCA with 44.1%; and SSRI, with 37.7%. SNRI also had the lowest discontinuation rates (26.1% versus 28.4% for SSRI, and 35.7% for TCA), suggesting superior benefit for the treatment of major depressive disorder (MDD).

Another economic assessment (Machado M *et al*, 2007b), developed with the purpose to determine the cost-effectiveness relationship of three antidepressant classes for the treatment of MDD in Brazil, assuming a 6-month treatment period, reported that SNRI represent a predominant strategy (offering greater efficacy at lower price), compared with SSRI and TCA.

Due to the increased pressure on healthcare expenses, resulting from current changes, it is appropriate to assess the health economic profile of new therapeutic options, aiming to optimize the use of healthcare resources and make expenses efficient, obtaining better results to benefit the population. The purpose of this study was to estimate the cost-effectiveness relationship of three therapeutic classes used in the treatment of MDD patients: SSRI, SNRI, and TCA, from the perspective of the ISSSTE.

Methodology

As established in the objectives of this study, it is necessary to carry out an assessment that compares two or more alternatives, considering both costs and consequences (Drummond MF *et al*, 1999). Therefore a full economic assessment or, more specifically, a cost-effectiveness assessment, is presented.

Target population

Patients ≥ 18 years of age diagnosed with moderate to severe MDD, with a score of 19 in HAMD scale, or a ≥ 18 score in the MADRS, without associated comorbidities or concomitant medications were analyzed.

Alternatives to be compared

The different types of antidepressants were classified according to their therapeutic class, as follows.

- Selective Serotonin Reuptake Inhibitors (SSRI): citalopram, escitalopram, fluoxetine, paroxetine and sertraline.
- Tricyclic antidepressants (TCA): amitriptyline and imipramine
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRI): duloxetine and venlafaxine

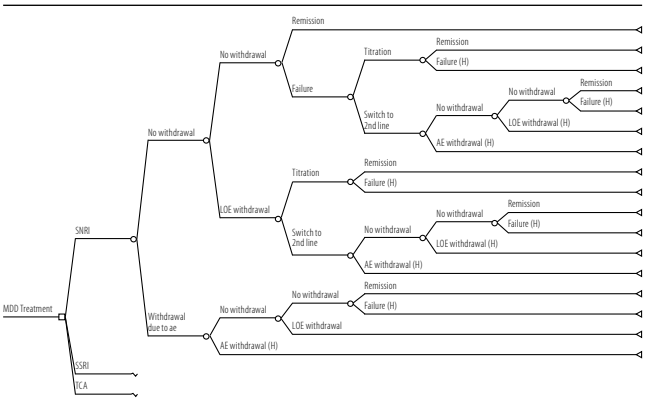
Cost-Effectiveness Analysis

A cost-effectiveness analysis of MDD treatment was developed considering the prescription of different antidepressants and the different therapeutic classes, SSRI, SNRI, and TCA.

For the economic assessment, a previously developed decision model (Machado M *et al*, 2007b) was adapted. In order to reflect the usual treatment practice of MDD treatment at the Institute for Social Security and Services for State Workers (ISSSTE), the treatment as well as transition probabilities of hypothetic patients from one class to another, were validated with a panel of experts including doctors from ISSSTE, using the Delphi methodology.

As MDD treatment in this study considered a 3-month period, a decision tree was used to evaluate health outcomes (this decision model is recommended in literature when short-term health results are analyzed), which is the best way to characterize the consequences and alternatives to represent the course of this type of patients (Raskati K, 2009; Drummond MF *et al*, 2008; DOF, 2010).

Figure 1 shows the structure of the decision tree used to assess both the cost results and cost effectiveness expected from MDD treatment. As it can be observed in Figure 1, the model shows 8 different paths defining possible outcomes from patients under treatment, considering the discontinuation rate due to intolerable adverse events (AE), remission, treatment failure and change in treatment. The probabilities of presenting these outcomes were determined by the efficacy reported in clinical trials, and were subsequently validated with an ISSSTE expert panel using the Delphi methodology. It was assumed that there was a 50% probability for hypothetic patients to require dose titration or changing to second line treatment in case of an inappropriate response to first line treatment. In addition, it was assumed that discontinuation due to AE would occur in the first two weeks of



MDD=Major depressive disorder; SNRI=Serotonin-norepinephrine reuptake inhibitors; SSRI= Selective serotonin reuptake inhibitors; TCA=Tricyclic antidepressants ;(H)=Hospitalization; AE=Adverse events; LE=Lack of efficacy. SSRI and TCA arms have the same treatment regimen and outcomes. Figure adapted from Machado *et al*. 2007

Figure I. Decision tree used in the three therapeutic classes in the treatment of MDD.

treatment, discontinuation due to lack of efficacy and remission, would occur four weeks after the treatment started. For those patients requiring hospitalization (in case of secondary therapeutic failure), an average stay of 28 days was assumed, and after this period patients would achieve clinical remission.

According to the panel of experts on MDD treatment, patients were monitored for a period of at least 4-6 weeks after initial treatment. Each time a patient started therapy (primary or secondary) and did not discontinue treatment, four visits to the second and third level specialist were considered before defining whether therapy had been successful. In case of discontinuation due to AE, patients would receive two weeks of treatment and five visits to the specialist before switching to another therapy. Since AE experienced by patients using antidepressants are minor (clinical grade 1-2; e.g., dry mouth, nausea, dizziness, headache, sweating, etc.), their costs were not included in this model.

According to recommendations of the expert panel, treatment algorithm considered for patients in the model was described as follows: patients treated with SNRI received SSRI as second line treatment; patients treated with SSRI received TCA as second line treatment; and those patients receiving TCA as first line therapy were switched to SSRI treatment.

Costs

Since the objective of this study was to assess the costs of antidepressants in ISSSTE, only direct medical costs were evaluated, including: i) acquisition costs of the therapeutic class, ii) additional expenses due to lack of efficacy or medical care related to AE; and iii) additional expenses due to treatment discontinuation. The costs of procedures and services were obtai-

ned using the unit price list according to the level of care published in the Mexican Federal Official Gazette (Diario Oficial de la Federación in 2010) (DOF, 2010); prices of the medication were obtained in the Government Purchase website COMPRANET. All prices and costs are expressed in 2010 US dollars.

In order to conduct the cost analysis according to the therapeutic class, a weekly mean dose for treatment was established for each class, as well as a weekly maximum mean dose, consistent with the prescribing information for each strategy. This dose was used for remissions with dose titration, and the value was multiplied by the cost per milligram corresponding to each medication, and the average of these values determined the price per therapeutic class. (Table 1).

Health outcomes

According to the model, discontinuation, remission, failure, hospitalization and change of treatment parameters were derived from items that have been published in the literature (Machado M *et al*, 2007b). In addition, the likelihood of change in treatment was validated by the panel of experts. The primary efficacy endpoint was remission rate defined as; i) score ≤ 7 in HAMD, or ii) score ≤ 12 in MADRS, measured ≥ 6 weeks after starting the therapy. A secondary efficacy endpoint was treatment tolerability, measured as discontinuation rate for AE and lack of efficacy.

Sensitivity analysis

A sensitivity analysis is required, since there is uncertainty concerning the estimations conducted in the construction of the decision models. Maximum and minimum values of costs are used as well as the probabilities within the decision model to determine the range of the results. Enough variability should be allowed to reflect realistic variations in the values (Rascati K, 2009). The deterministic approach to sensitivity deterministic consisted of a series of univariate analyses. Results are presented in a tornado diagram. Analyses were conducted in the TreeAge Pro Suite 2010® software (TreeAge Software Inc., Williamstown, MA, USA)

Results (Base case)

Within the three therapeutic classes assessed, expected cost for one patient treated with each of the three options were $5,001; $4,215; $4,078 for SSRI, TCA, and SNRI, respectively. The alternative with greater expected remission rate was the SNRI class.

For each thousand patients treated with SNRI instead of TCA, there would be $68,272 cost savings over a period of 3 months. Likewise, when compared with SSRI, savings generated by SNRI were more than $367,437 for every thousand treated patients.

Table I. Cost of medications and doses used in the economic assessment (2010 USD)

	Capsules	Mg	Price/mg	DDD Average	DDD Maximum Average	Cost/week	Maximum cost/week
SNRI							
Duloxetine	28	60	$ 0.036	60	120	$ 15.0	$ 29.9
Venlanfaxine	10	75	$ 0.028	150	225	$ 29.2	$ 43.8
Average			$ -			**$ 22.1**	**$ 36.9**
SSRI			$ -				
Citalopram	14	20	$ 0.034	20	60	$ 4.7	$ 14.2
Escitalopram	14	10	$ 0.243	10	20	$ 17.0	$ 34.0
Fluoxetine	14	20	$ 0.002	20	80	$ 0.2	$ 1.0
Paroxetine	10	20	$ 0.064	20	50	$ 9.0	$ 22.6
Sertraline	14	50	$ 0.005	50	200	$ 1.9	$ 7.7
Average			$ -			**$ 6.6**	**$ 15.9**
TCA			$ -				
Amitriptiline	20	25	$ 0.001	150	200	$ 1.2	$ 1.6
Imipramine	20	25	$ 0.002	150	200	$ 2.0	$ 2.7
Average			$ -			**$ 1.6**	**$ 2.1**

***Defined daily dose; †Milligrams: Exchange Rate: 1USD:12.50 MXN Pesos**

Source: Transparence portal of Mexican Institute of Social Security (IMSS)

Table II. Parameters used in the decision analytic model (2010, USD)

Parameter	Base case	Minimum value	Maximum value	Reference
Probability of Tx discontinuation due to AE				
SNRI	0.103	0.063	0.143	
SSRI	0.083	0.047	0.119	(Machado M *et al*, 2007a)
TCA	0.198	0.136	0.261	
Probability of remission				
SNRI	0.49	0.407	0.573	
SSRI	0.377	0.269	0.486	(Machado M *et al*, 2007a)
TCA	0.441	0.354	0.527	
Probability of discontinuation due to LE				
SNRI	0.062	0.028	0.096	
SSRI	0.072	0.032	0.111	(Machado M *et al*, 2007a)
TCA	0.099	0.029	0.169	
Probability of change to second line treatment	0.5	0.5 – 1.00	Beta	(Machado M *et al*, 2007a)
Treatment cost data (2010 USD)				
SNRI	22	29.48	36.88	
SSRI	6.6	11.24	15.92	
TCA	1.6	1.88	2.16	
Additional cost in patients with Intolerable AE or LE	109	98.06	119.85	

Tx: Treatment; AE: Adverse events; LE: Lack of efficacy; SNRI=Serotonin-norepinephrine reuptake inhibitors; SSRI= Selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressants. Exchange Rate: 1USD:12.50 MXN Pesos

Results of TCA administration costs were significantly lower than those of SNRI. However, superior efficacy of SNRI provided a better cost-effectiveness ratio.

Sensitivity analysis

For the sensitivity analysis, results of a meta-analysis update (Machado M & Einarson TR, 2010) were considered for the scenario. These data were not considered for the base case analysis, as this comparison does not include the TCA group. Figure 2 shows the result of the sensitivity analysis in the Tornado Cost-Effectiveness Ratio diagram. The Tornado analysis compares the impact of several univariate sensibility analyses involving all variables. However, for simplification purposes, only those of greater impact on the results are shown, represented by the first bar, i.e., for SNRI versus SSRI, it is the probability of remission using TCA. For SNRI versus TCA, it is the probability of discontinuation due to SNRI adverse events. In both cases, the variable that plays an important role is the probability of change in treatment resulting from a partial response that was assumed (50%) for all therapeutic classes. The range shown in the left box corresponds to the values expected for each parameter.

Table III. Cost-effectiveness study results (2010 USD)

Strategy	Cost†	Effectiveness†*	ICER
SNRI	$4,078,659	649	Baseline
SSRI	$4,215,944	585	Dominated‡
TCA	$5,001,560	602	Dominated‡

†Expressed by 1,000 patients. *Expressed as the number of patients who achieved remission rate. ‡More expensive and less effective strategy. Exchange Rate: 1USD:12.50 MXN Pesos

Discussion

The result of this analysis suggests that the SNRI group, as a therapeutic class for MDD management, is a strategy that provides greater effectiveness at a lower cost, i.e., a

dominant alternative. More importantly, the prices of medications considered within the TCA therapeutic class are generic, thus the price of a generic is regarded in the analysis. . However, due to the effectiveness associated to SNRI, it is observed that in the long run the costs associated to this group are significantly lower. These results are similar to those presented by Machado *et al*., where SNRI are presented as a dominant therapy, associated to a better response rate defined as the expected remission rate compared to the SSRI and TCA groups.

To date, no complete economic assessments of MDD therapeutic classes have been found in Mexico. However, published information on assessments performed in other countries is extensive. Most of these analyses use clinical response rate as the primary efficacy measurement. However, in this study, clinical remission rate was used, which is the fundamental efficacy measurement in the treatment of MDD.

References

American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders. Fourth ed. 2000, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association.

Birnbaum HG, Ben-Hamadi R, Greenberg PE, Hsieh M, Tang J, Reygrobellet C. Determinants of direct cost differences among US employees with major depressive disorders using antidepressants. Pharmacoeconomics. 2009;27(6):507-17

Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. Oxford, Oxford University Press, 2007.pp 22-23.

Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA. 1990 Nov 21;264(19):2524-8.

Costos unitarios por nivel de atención médica para el año 2010. Diario Oficial de la Federación 18 de mayo del 2010. Disponible en línea: http://www.imss.gob.mx/NR/rdonlyres/4D2C6F5A-2B87-483C-9B8F-F142B70669F2/0/4134.pdf

Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Second edition. Oxford:Oxford University Press; 1999.

Fautrel B, Guillemin F. Cost of illness studies in rheumatic diseases. Curr Opin Rheumatol. 2002;14:121-126.

Frasure-Smith N, Lespérance F, Talajic M. Depression Following Myocardial Infarction, Impact on 6-Month Survival. JAMA. 1993;270(15):1819-1825

Greco T, Eckert G, Kroenke K. The outcome of physical symptoms with treatment of depression. J Gen Intern Med.2004;19(8):813-818

Greden GF. Physical Symptoms in Depression: Unmet Needs. Journal of Clinical Psychiatry. 2003, 64 (Suppl. 7),5-11.

Greenberg PE, Stiglin LE, Finkelstein SN, Berndt ER. The economic burden of depression in 1990. J Clin Psychiatry. 1993;54:405-418.

Jeannette R. Ickovics, Merle E. Hamburger, David Vlahov, Ellie E. Schoenbaum, Paula Schuman, Robert J. Boland, Janet Moore, Mortality, CD4 Cell Count Decline, and Depressive Symptoms Among HIV-Seropositive Women. JAMA. 2001;285(11):1466-1474

Judd LL, et al. Does Incomplete Recovery From First Lifetime Major Depressive Episode Heralda Chronic Course of Illness? Am J Psychiatry. 2000.; 157: 1501-1504.

Lustman P J, Anderson R J, Freedland K E, de Groot M, Carney R M, Clouse R E. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care July 2000 vol. 23 no. 7 934-942

Machado M, Einarson TR. Comparison of SSRIs and SNRIs in major depressive disorder: a meta-analysis of head-to-head randomized clinical trials. Journal of Clinical Pharmacy and Therapeutics. 2010. 35 Apr(2), pages 177–188.

a) Machado M, Iskedjian M, Ruiz I, Einarson TR. Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. Curr Med Res Opin. 2006 Sep;22(9):1825-37.

b) Machado M, Iskedjian M, Ruiz I, Einarson TR. The economic impact of introducing serotonin-noradrenaline reuptake inhibitors into the Brazilian national drug formulary: cost-effectiveness and budget-impact analyses. Pharmacoeconomics. 2007;25(11):979-90.

Mary de Groot, Ryan Anderson, Kenneth E. Freedland, Ray E. Clouse and Patrick J. Lustman, Association of Depression and Diabetes Complications: A Meta-Analysis. Psychosomatic Medicine 63:619-630 (2001)

McCunney RJ. Health and productivity: a role for occupational health professionals. J Occup Environ Med. 2001;43:30-35.

Medina-Mora ME, Borges G, Lara Muñoz C, et al. Prevalencia de Trastornos Mentales y Uso de Servicios: Resultados de la Encuesta Nacional de Epidemiología Psiquiátrica en México. Salud Mental. 2003, 26(4),1-16.

Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry. 1998. 59(11):608-619.

Muñoz R. McBride ME, Brnabic JM, Carlos J. López , Luiz Alberto B. Hetem , Ricardo Secin ,Héctor J. Dueñas. Major depressive disorder in Latin America: The relationship between depression severity, painful somatic symptoms, and quality of life. Journal of Affective Disorders. 2005. 86 93–98.

Pierre V. Tran, Frank P. Bymaster, Robert K. McNamara, and William Z. Potter, Dual Monoamine Modulation for Improved Treatment of Major Depressive Disorder. J Clin Psychopharmacol. 2003;23: 78–86.

Rascati K. Essentials of Pharmacoeconomics. Lippincott Williams & Wilkins, 2009. 136-137.

Riedel JE, Baase C, Hymel P, Lynch W, Dreisbach S, Peterson KW. Preventing Disease and Promoting Health: Impact on Productivity. Scottsdale, Ariz:Institute for Health and Productivity Management;2001.

Rohde P, Lewinsohn PM, Tilson M, Seeley JR. 58. Dimensionality of coping and its relation to depression. J Pers Soc Psychol. 1990 Mar;58(3):499-511.

Ronald C. Kessler, Patricia Berglund, Olga Demler, MS, Robert Jin, MA, Doreen Koretz, Kathleen R. Merikangas, A. John Rush, MD, Ellen E. Walters, MS, Philip S. Wang, The Epidemiology of Major Depressive Disorder. JAMA. 2003.289:3095-3105.

Simon GE, Barber C, Birnbaum HG, et al. Depression and work productivity: the comparative costs of treatment versus nontreatment. J Occup Environ Med.2001;43:2-9.

Simon GE, Revicki D, Heiligenstein J, et al. Recovery from depression, work productivity, and health care costs among primary care patients. Gen Hosp Psychiatry.2000;22:153-162.

Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, Coryell W,

Warshaw M, Turvey C, Maser JD, Endicott J. Multiple Recurrences of Major Depressive Disorder. Am J Psychiatry. 2000. 157:229-233

Stewart WF, Ricci JA, Chee E, Hahn SR, Morganstein D. Cost of lost productive work time among US workers with depression. JAMA. 2003 Jun 18;289(23):3135-44.

Susan A. Everson, Robert E. Roberts, Debbie E. Goldberg, George A. Kaplan, Depressive Symptoms and Increased Risk of Stroke Mortality Over a 29-Year Period. Arch Intern Med. 1998.;158:1133-1138.

Thase ME, Entsuah AR, Rudolph RL Meta-analyis of SSRI and Venlafaxine efficacy in double blind, placeco controlled tirals. British Journal of Psychiatry (2001) 178, 234–241.

Thase ME, Simons AD, McGeary J, Cahalane JF, Hughes C, Harden T and Friedman E. Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. Am J Psychiatry. 1992.; 149:1046-1052

Trivedi, A. John Rush, Stephen R. Wisniewski, Andrew A. Nierenberg, Diane Warden, Louise Ritz, Grayson Norquist, Robert H. Howland, Barry Lebowitz, Patrick J. McGrath, Kathy Shores-Wilson, Melanie M. Biggs, G. K. Balasubramani, and Maurizio Fava, Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. Am J Psychiatry. 2006.163:28-4.

Ustün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. Br J Psychiatry. 2004 May;184:386-92.

World Health Organization, Revised global burden of disease (GBD) 2002 estimates. Disponible en http://www.who.int/healthinfo/bodgbd2002revised/en/index.html.2005

World Health Organization. Burden of disease. Disponible en: http://www.wpro.who.int/NR/rdonlyres/2FACBCE6-0713-4604-BCF1-2BE9B6E83AC9/0/11_Chapter6Burdenofdisease.pdf

Zeiss AM, Lewinsohn PM. Enduring deficits after remissions of depression: a test of the scar hypothesis. Behav Res Ther. 1988;26(2):151-8.