

Genetic Testing for CYP-2D6 Polymorphism Prior to Selective Serotonin Reuptake Inhibitor Prescribing: Results from a Decision Analysis Model

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Abstract

Objective: The objective of this paper is to estimate the cost-effectiveness of CYP-2D6 metabolic genetic testing when choosing between two selective serotonin uptake inhibitors using a decision analysis model.

Methods: The model considers the impact of treatment-related adverse drug reactions, adherence, and outcomes. Simulations of 10,000 hypothetical subjects were used to assess the variability of costs and effects over the stochastic parameters in the model and a series of one-way sensitivity analyses identified key variables that may influence the results.

Results: The model demonstrates that both the gene chip citalopram arm and the paroxetine with no gene chip arm are costlier and less effective (dominated) compared to the citalopram with no gene chip arm. Based on probabilistic sensitivity analysis and variation of key decision-making variables, the findings were robust to the assumptions of the model.

Conclusions: Across a wide range of assumptions this model shows that genetic testing for CYP-2D6 polymorphisms prior to initial selection of citalopram or paroxetine to treat depression is not cost-effective.

Introduction

Depression is common and expensive in terms of disease burden and treatment costs in the United States. More specifically, lifetime prevalence estimates for major depression vary between 13% to 16% [1,2] and estimated total costs associated with depression were \$210.5 billion in 2010 (45% direct costs, 5% suicide-related costs, and 50% to workplace costs) [3]. Efficacious antidepressant agents are available in multiple drug classes [4-6]. The American Psychiatric Association (APA) guidelines encourage physicians to consider adverse effects, safety and tolerability, patient preference, results of clinical trials, and costs when prescribing an antidepressant [7]. Currently, genetic testing to determine

metabolic genotypes is not widely utilized but it does provide an avenue to personalize pharmacotherapy decisions for depression.

One of the primary predictors of antidepressant non-response is antidepressant non-adherence, [8-10] and the primary predictor of antidepressant non-adherence is Adverse Drug Reactions (ADRs) [9]. ADRs can result from genetic and non-genetic factors (e.g. age, drug and dietary interactions) [11,12]. One of the most anticipated benefits of pharmacogenetics is the reduction in the incidence of ADRs. In vitro diagnostic tests may be useful in identifying persons who are more likely to have ADRs from particular drugs because of genetic variations in the enzymes that metabolize drugs [13]. Even small reductions in the rate of ADRs

could improve health outcomes and reduce health care costs [14].

Despite excitement over the prospect of precision medicine in psychiatry, the evidence base for when to use genetic testing to guide antidepressant medication selection and dosing decisions is under-developed [15-21]. The challenges unique to the treatment of psychiatric disorders have made decisions around implementing these types of tests difficult [22-24]. Yet, interest in genetic testing to inform prescribing of antidepressants remains [25]. For example, genetic testing for Cytochrome P450 (CYP) polymorphisms, which metabolize Selective Serotonin Reuptake Inhibitors (SSRIs) and other antidepressants, [26] may allow for better initial treatment recommendations. Many questions remain about the utility and specifically the cost-effectiveness of utilizing this technology [15,19]. While the cost of genetic testing is expensive, it is decreasing, [27] still, it is unclear at what price testing becomes cost-effective.

The objective of this paper is to estimate the cost-effectiveness of metabolic genetic testing to identify CYP-2D6 polymorphisms using a decision analysis model. This study examines one specific clinical situation, in which a practitioner is deciding between two treatment strategies for the treatment of depression in patients previously unexposed to antidepressant pharmacotherapy. The model compares the costs and effects for genetic testing versus no testing prior to initiating either citalopram or paroxetine. Sensitivity analyses take into account a range of probabilities for CYP-2D6 polymorphisms, side effects, adherence, outcomes, and genetic testing cost.

Methods

A decision analysis model was developed to estimate the cost-effectiveness of genetic testing prior to initiation of either citalopram or paroxetine for the treatment of depression in patients who were previously unexposed to antidepressant pharmacotherapy. The model was constructed from the payer's perspective with cost estimates derived from a large, nationally representative (US), employer-sponsored, managed-care database. The model considers the impact of treatment-related ADRs, medication adherence, and treatment outcomes. To develop the model, a literature review identified existing cost-effectiveness models that to explore the cost-effectiveness of pharmacologic treatments for depression. Based on the available literature, the decision model published by Sullivan, et al. [28] (henceforth 'Sullivan') was selected because it included the most detailed summary of antidepressant treatment ADRs, adherence, and treatment outcomes [28-31]. The decision analysis model for the current study replicated and validated Sullivan using Tree Age Pro [32]. Changes were made to update and adapt the Sullivan Model to current practice; these changes are noted in the following sections.

Pharmacogenetic Model

While Sullivan included the eight most commonly prescribed serotonin reuptake inhibitors, including SSRIs and se-

rotonin norepinephrine reuptake inhibitors, [7] the current study focuses exclusively on citalopram and paroxetine because of their high rates of use, differing (and known) metabolic profiles, and generic availability. A sample of the resulting model can be seen in Figure 1. Moving from left to right, the order of the model was assignment to either citalopram or paroxetine, treatment response, ADR, response to ADR, and treatment outcome.

Three treatment strategies were modeled: (1) initiate treatment with paroxetine, (2) initiate treatment with citalopram, and (3) conduct a genetic test for CYP-2D6 polymorphisms where fast metabolizers are prescribed paroxetine and slow metabolizers are prescribed citalopram. Successful therapeutic response was defined as the combination of (1) a reduction of 50% in baseline Montgomery-Asberg Depression Rating Scale (MADRS) score [33] by week 8 and (2) completion of 180-day course of SSRI therapy as outlined by the APA guidelines [34]. Efficacy of citalopram and paroxetine was assumed to be 60% based on previous literature [35,36].

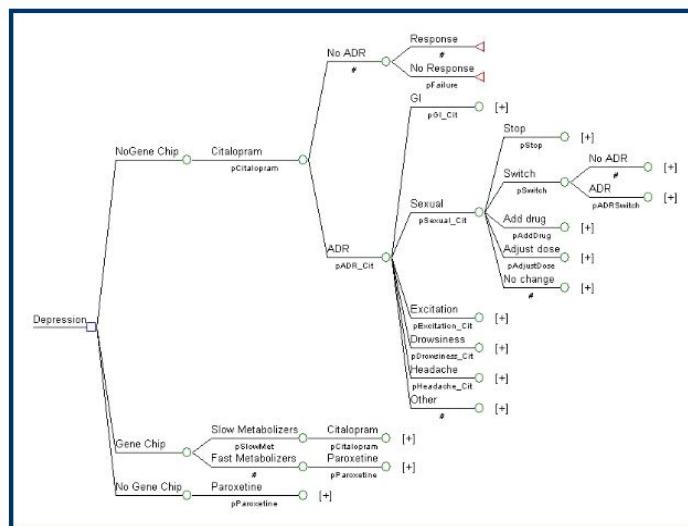


Figure 1: Sample of Decision Tree Structure.

Time Horizon

The model used an overall time horizon of six months to incorporate all costs and utilities, which is consistent with previous economic analyses [30,37]. The time horizon for drug stoppage because of therapeutic failure or ADR occurrence was three months, based on a retrospective analysis of managed care claims that suggested average stoppage of SSRIs occurs at three months [37]. The time horizon for ADRs varied from three to six months depending on possible treatment response and ADRs.

ADR Incidence Rates

A literature search did not identify head-to-head clinical trials to compare ADRs across all serotonin reuptake inhibitors.

Thus, the differential ADR rates described by Sullivan assessing the placebo-corrected incidence of ADRs from the FDA approved labeling for the SSRIs were used. Sullivan varied incidence estimates of all ADRs by $\pm 25\%$ in a Bayesian second-order Probabilistic Sensitivity Analysis (PSA). The influence of these estimates was reviewed in both univariate and multivariate likelihood threshold analyses.

For the base-case estimates, ADR incidence data from all placebo-controlled clinical trials included in the FDA approved labeling of each SSRI was pooled. Because SSRIs are used for a variety of indications and there is substantial overlap, all available trials across all indications comparing an individual SSRI with placebo were used to derive a measure of the relative incidence of ADRs. This was accomplished by calculating a sample size weighted average

ADR incidence for each SSRI-placebo pair. The incidence of each ADR was then converted to number of ADRs per 100 patients. The total number of ADRs was placebo-corrected by subtracting the total expected ADRs in the placebo group from that of the drug to derive the number attributable to each SSRI.

Next, the placebo-corrected ADR incidence rate for each SSRI was compared with the average across all serotonin reuptake inhibitors to estimate the relative percent of ADRs attributable to each drug. The average probability of developing a treatment-emergent ADR requiring a physician visit while on SSRI therapy was determined by multiplying the relative, placebo-corrected percentage of ADRs for each agent by 41% i.e., percentage of patients experiencing at least one SSRI related ADR [38]. The model also estimated treatment options for SSRI-related ADRs and respective probabilities for switching to a new drug. In the current model, the experience of ADRs was moved ahead of treatment response in order to be more consistent with the clinical course of antidepressant treatment.

Metabolic Levels

Persons were categorized into two levels of metabolism for the 2D6 enzyme (poor/intermediate, extensive/ultra-rapid). Relative risk of ADRs between poor/intermediate and extensive/ultra-rapid metabolizers of paroxetine was calculated from Table 2 of Murphy et al. (2003) [39]. The matrix of probabilities for each of the polymorphism combinations was based on results from the STAR*D depression treatment trial [40]. The matrix includes antidepressant options for each cell to maximize tolerability using the results of genetic testing. Key model inputs are found in Table 2.

Costs and Utility

Direct medical costs included the drug cost of the SSRI, the costs of medical office visits, costs of treatment failure, costs at-

tributable to SSRI-related ADRs. All costs were taken from sources similar to those available to Sullivan and inflated to 2016 dollars using the medical component of the Consumer Price Index. As in Sullivan, costs attributable to SSRI-related-ADRs included costs of additional medical office visits and drugs to treat ADRs as well as costs of treatment failure for patients who discontinued treatment. Patients were classified as treatment resistant or treatment failure if: (1) they switched to another agent two or more times because of ADRs; (2) they discontinued treatment because of ADRs; (3) they switched to another agent two or more times because of non-response; or (4) they did not respond to the initial SSRI. Monthly drug costs for SSRIs and for treating SSRI-related ADRs were based on the Federal Upper Limit amount for each drug listed in 2010. Medical office visits were based on 2011 average reimbursement rates for physician by the Center for Medicare and Medicaid Services. All outcomes are reported in quality-adjusted life years QALYs from the literature based on level of treatment response [41,42]. The cost of conducting genetic testing for CYP-2D6 was estimated to be \$98.77 per patient [43].

In addition to examining direct costs, Sullivan incorporated the impact of ADRs on the effectiveness of treatment using QALYs [44]. Utility values for each health state were derived from a direct analysis of the 2000 Medical Expenditure Panel Survey (MEPS). MEPS is a nationally representative survey of the civilian non-institutionalized US population and is available at www.meps.ahrq.gov/mepsweb/ [45,46].

Sensitivity Analysis

All probability, cost, and utility parameters were assumed to be stochastic. Specific probability distributions were chosen to reflect reasonable values for probabilities, ADR incident rates, costs and utilities. Probabilities, incidence rates, and utilities were assumed to follow beta-distributions; costs were assumed to be normally distributed; utilization measures were assumed to be gamma distributed. Relative risk of ADRs between poor/intermediate and extensive/ultra-rapid metabolizers of paroxetine were assumed to be log-normal distributions [47]. Base-case placebo response rate (as a proportion) was derived from a review study by Walsh et al [48] and was assumed to have a normal distribution. In order to construct a range, the base-case value was varied to incorporate the uncertainty surrounding these estimates as in Sullivan. All cost values were varied $\pm 25\%$ in the PSA. Simulation of 10,000 subjects were used to assess the variability of costs and effects over the stochastic parameters in the model. Additionally, a series of one-way sensitivity analyses of variables important to clinical or policy decision making were conducted.

Results

The base-case results are presented in Table 1 and base-case

inputs are listed in the second column of Table 2. The base-case results demonstrate that both the gene chip arm and the paroxetine with no gene chip arm are costlier and less effective (dominated) when compared to the citalopram with no gene chip arm. Therefore, in the base-case, initiating treatment with citalopram is the preferred option over genetic testing.

Strategy	Cost, \$ (95% CI)	Effectiveness, QALY (95% CI)	Incremental Cost-Effectiveness Ratio
No Gene Chip - Citalopram	4,393 (343 - 10,121)	0.378 (0.331 - 0.394)	--
Gene Chip	4,555 (389 - 10,337)	0.376 (0.331 - 0.394)	Dominated
No Gene Chip - Paroxetine	4,484 (291 - 10,326)	0.372 (0.318 - 0.394)	Dominated

Table 1: Base-case Estimates.

Variable	Base-case	Sensitivity Range	Lower Bound	Upper Bound	Gene Chip Threshold**
			ICER*	ICER*	
Citalopram Monthly Cost	\$42	\$0-\$200	Citalopram:	Paroxetine	\$98-\$200
			Gene Chip: Dominated	Gene Chip: \$36,987/QALY	
			Paroxetine: Dominated	Citalopram: \$286,998/QALY	
Adverse Drug Reaction (ADR) Duration (Months)	1	0.50-2.00	Citalopram:	Citalopram	
			Gene Chip: Dominated	Gene Chip: \$27,648/QALY	
			Paroxetine: Dominated	Paroxetine: \$4,338/QALY	
Paroxetine Monthly Cost	\$34	\$0-\$200	Citalopram:	Citalopram	
			Gene Chip: Dominated	Gene Chip: Dominated	
			Paroxetine: Dominated	Paroxetine: Dominated	
Cost of Gene Chip	\$99	\$0-\$400	Citalopram:	Citalopram	
			Gene Chip: Dominated	Gene Chip: Dominated	
			Paroxetine: Dominated	Paroxetine: Dominated	
Cost of Therapy Failure	\$9,688	\$2,000-\$16,000	Citalopram:	Citalopram	
			Gene Chip: Dominated	Gene Chip: Dominated	

			Paroxetine: Domi-nated	Paroxetine: Domi-nated	
Odds Ratio ADR for Slow Metabolizers Treated with Paroxetine	1.52	1.00-3.00	Citalopram:	Citalopram	
			Gene Chip: Domi-nated	Gene Chip: \$142,054/ QALY	
			Paroxetine: Domi-nated	Paroxetine: Domi-nated	
Citalopram ADR	0.22	0.10-0.35	Citalopram:	Citalopram	
			Gene Chip: Domi-nated	Gene Chip: \$521,478/ QALY	
			Paroxetine: Domi-nated	Paroxetine: Domi-nated	
Probability of Treatment Failure	0.4	0.20-0.79	Citalopram:	Citalopram	
			Gene Chip: Domi-nated	Gene Chip: Domi-nated	
			Paroxetine: Domi-nated	Paroxetine: Domi-nated	
Probability of Slow Metabolizer	0.25	0.22-0.29	Citalopram:	Citalopram	
			Gene Chip: Domi-nated	Gene Chip: Domi-nated	
			Paroxetine: Domi-nated	Paroxetine: Domi-nated	
Utility of Therapy Failure	0.73	0.37-0.90	Citalopram:	Citalopram	
			Gene Chip: Domi-nated	Gene Chip: Domi-nated	
			Paroxetine: Domi-nated	Paroxetine: Domi-nated	
Cost of Physician Visit	\$89	\$31-\$126	Citalopram:	Citalopram	
			Gene Chip: Domi-nated	Gene Chip: Domi-nated	
			Paroxetine: Domi-nated	Paroxetine: Domi-nated	
Paroxetine ADR	0.5	0.10-0.75	Citalopram:	Citalopram	
			Gene Chip: Domi-nated	Gene Chip: Domi-nated	
			Paroxetine: Domi-nated	Paroxetine: Domi-nated	

*ICER stands for Incremental Cost-Effectiveness Ratio.

**Values of variable for which Gene Chip is optimal.

Table 2: One-way Sensitivity Analyses.

The one-way sensitivity analyses suggest circumstances in which genetic testing for CYP polymorphisms may be a cost-effective strategy. Assuming a \$50,000 per QALY cost-effectiveness threshold, the gene chip arm is preferred only when the monthly cost of citalopram is above \$98. No other analyses within the sensitivity ranges of the identified variables contained conditions where the gene chip was preferred.

Discussion

The choice of citalopram without genetic testing is the dominant strategy over a wide range of conditions. This finding is largely because of citalopram having a price comparable to that of paroxetine, and having lower ADR rates than paroxetine. Therefore, initiating citalopram is the preferred treatment strategy over genetic testing or initiating treatment with paroxetine. The base-case provides a straightforward example of a clinical situation where genetic testing is not an efficient use of resources, the important. The important takeaway for clinicians is the robustness of these findings. Wide variation of the costs of either medication or the cost of the genetic testing does not affect the preferred choice of treatment.

While the findings are not applicable outside the bounds of these assumptions, this study highlights the need for careful consideration before implementation of genetic testing in any given clinical situation. Moreover, this methodology could be applied to new antidepressant medications coming on the market. For example, if new and more expensive (i.e., \$98 or more per month) antidepressant medications with low ADR rates become available, genetic testing may allow clinicians to steer patients towards less expensive generically available antidepressant medications if patients are not slow metabolizers.

Limitations

There are limitations associated with this model. The evidence linking ADR rates of paroxetine or other SSRIs to CYP-2D6 polymorphisms is not well established and this model does not extend to other CYP polymorphisms. This modeling strategy did not incorporate all SSRIs as possible comparators; however, it is unlikely that including other treatment options would yield different conclusions regarding genetic testing given that all have similar rates of effectiveness when used as first-line treatment and all have similar costs.

Conclusions

Genetic medicine holds great promise for personalizing treatment and improving outcomes. The citalopram versus paroxetine decision model presented here demonstrated no cost or effectiveness advantage for using CYP-2D6 genetic testing. Decision analysis models provide an opportunity to estimate the cost-effectiveness of genetic testing across a wide variety of scenarios.

References

1. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, et al. (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 289: 3095-3105.
2. Hasin DS, Goodwin RD, Stinson FS, Grant BF (2005) Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry* 62: 1097-1106.
3. Greenberg PE, Fournier A-A, Sisitsky T, Pike CT, Kessler RC (2015) The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *The Journal of clinical psychiatry* 76: 155-162.
4. Anderson IM (2000) Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord* 58: 19-36.
5. Song F, Freemantle N, Sheldon TA, A House, P Watson, et al. (1993) Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *British Medical Journal* 306: 683-687.
6. Geddes JR, Freemantle N, Mason J, Eccles MP, Boynton J (2007) Selective serotonin reuptake inhibitors (SSRIs) versus other antidepressants for depression. *Cochrane Database of Systematic Reviews* 18: CD001851.
7. American Psychiatric Association (2000) Practice Guideline for the Treatment of Patients with Major Depressive Disorder (Revision). *American Journal of Psychiatry* 157: 1-45.
8. Lin EH, Von Korff M, Katon W, Bush T, Simon GE, et al. (1995) The role of the primary care physician in patients' adherence to antidepressant therapy. *Medical Care* 33: 67-74.
9. van Geffen EC, van der Wal SW, van Hulten R, de Groot MC, Egberts AC, et al. (2007) Evaluation of patients' experiences with antidepressants reported by means of a medicine reporting system. *Eur J Clin Pharmacol* 63: 1193-1199.
10. Bambauer KZ, Adams AS, Zhang F, Minkoff N, Grande A, et al. (2006) Physician alerts to increase antidepressant adherence: fax or fiction? *Arch Intern Med* 166: 498-504.
11. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W (2001) Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *Jama* 286: 2270-2279.
12. Rasmussen-Torvik LJ, McAlpine DD (2007) Genetic screening for SSRI drug response among those with major depression: great promise and unseen perils. *Depress Anxiety* 24: 350-357.
13. Secretary's Advisory Committee on Genetics HaS. Realizing the potential of pharmacogenomics: Opportunities and challenges. Department of Health and Human Services 2008.
14. Ernst FR, Grizzle AJ (2001) Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash)* 41: 192-199.
15. Mrazek DA (2006) Incorporating pharmacogenetics into clinical practice: reality of a new tool in psychiatry. The context of genetic testing in clinical psychiatric practice. *CNS Spectr* 11: 3-4.
16. Merikangas KR, Risch N (2003) Will the genomics revolution revolutionize psychiatry? *Am J Psychiatry* 160: 625-635.

17. Gardiner SJ, Begg EJ (2006) Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. *Pharmacol Rev* 58: 521-590.
18. de Leon J, Armstrong S, Cozza K (2006) Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics* 47: 75-85.
19. Arranz MJ, de Leon J (2007) Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry* 12: 707-747.
20. EGAPP Working Group (2007) Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. *Genet Med* 9: 819-825.
21. Thakur M, Grossman I, McCrory DC, Orlando LA, Steffens DC, et al. (2007) Review of evidence for genetic testing for CYP450 polymorphisms in management of patients with nonpsychotic depression with selective serotonin reuptake inhibitors. *Genet Med* 9: 826-835.
22. Nassan M, Nicholson WT, Elliott MA, Vitek CRR, Black JL, et al. (2016) Pharmacokinetic pharmacogenetic prescribing guidelines for antidepressants: a template for psychiatric precision medicine. *Mayo Clinic Proceedings* 91: 897-907.
23. Dubovsky SL (2016) The Limitations of Genetic Testing in Psychiatry. *Psychotherapy and psychosomatics* 85: 129-135.
24. Hamilton SP (2015) The promise of psychiatric pharmacogenomics. *Biological psychiatry* 77: 29-35.
25. de Leon J, Armstrong SC, Cozza KL (2006) Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics* 47: 75-85.
26. Matchar DB, Thakur ME, Grossman I, McCrory DC, Orlando LA, et al. (2007) Testing for Cytochrome P450 Polymorphisms in Adults with Non-Psychotic Depression Treated with Selective Serotonin Reuptake Inhibitors. *Evidence Report/Technology Assessment* No 146: 1-77.
27. Nebert DW, Zhang G, Vesell ES (2009) From human genetics and genomics to pharmacogenetics and pharmacogenomics: past lessons, future directions. *Drug Metab Rev*, 2008 40: 187-224.
28. Sullivan PW, Valuck R, Saseen J, MacFall HM (2004) A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions. *CNS Drugs* 18: 911-932.
29. Doyle JJ, Casciano J, Arikian S, Tarride JE, Gonzalez MA, et al. (2001) A multinational pharmacoeconomic evaluation of acute major depressive disorder (MDD): a comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs. *Value Health* 4: 16-31.
30. Lenox-Smith A, Conway P, Knight C (2004) Cost effectiveness of representatives of three classes of antidepressants used in major depression in the UK. *Pharmacoeconomics* 22: 311-319.
31. Hemels ME, Kasper S, Walter E, Einarson TR (2004) Cost-effectiveness of escitalopram versus citalopram in the treatment of severe depression. *Ann Pharmacother* 38: 954-960.
32. TreeAge Pro 2013 [computer program]. Williamstown, MA: TreeAge Software, Inc.; 2013.
33. Montgomery SA, Asberg M (2000) Montgomery-Asberg Depression Rating Scale (MADRS). In: Association AP, ed. *Handbook of Psychiatric Measures*. Washington, DC: American Psychiatric Association, 2000.
34. Association AP (2006) American Psychiatric Association Practice Guidelines for the treatment of psychiatric disorders: compendium, American Psychiatric Pub.
35. Bull SA, Hunkeler EM, Lee JY, Rowland CR, Williamson TE, et al. (2002) Discontinuing or switching selective serotonin-reuptake inhibitors. *Annals of Pharmacotherapy* 36: 578-584.
36. Masand PS (2003) Tolerability and adherence issues in antidepressant therapy. *Clin Ther* 25: 2289-2304.
37. Valuck R (2002) Treatment of depression with citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine in managed care: part I. drug selection, dosing, and utilization. *Drug Benefit Trends* 14: 23-30.
38. Rascati KL, Godley P, Pham H (2001) Evaluation of resources used to treat adverse events of selective serotonin reuptake inhibitor use. *Journal of Managed Care Pharmacy* 7: 402-406.
39. Murphy Jr GM, Kremer C, Rodrigues HE, Schatzberg AF (2014) Pharmacogenetics of antidepressant medication intolerance. *American Journal of Psychiatry*.
40. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, et al. (2004) Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Controlled clinical trials* 25: 119-142.
41. Pyne JM, Bullock D, Kaplan RM, Thomas L Smith, J Christian Gillin, et al. (2001) Health-related quality-of-life measure enhances acute treatment response prediction in depressed inpatients. *J Clin Psychiatry* 62: 261-268.
42. Pyne JM, Patterson TL, Kaplan RM, Gillin JC, Koch WL, et al. (1997) Assessment of the quality of life of patients with major depression. *Psychiatr Serv* 48: 224-230.
43. Chen S, Chou WH, Blouin RA, Mao Z, Humphries LL, et al. (1996) The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry. *Clinical Pharmacology & Therapeutics* 60: 522-534.
44. Gold MR, Siegel JE, Russell LB, Weinstein MC (1996) *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press, Inc.
45. Services USDHaH (1980) *International classification of diseases: 9th revision: Clinical modification (ICD-9-CM)*, Volume 1: Diseases Tabular List. 2 ed. Washington, D.C.: U.S. Government Printing Office.
46. Elixhauser A, Andrews RM, Fox S (1993) Clinical classifications for health policy research: Discharge statistics by principal diagnosis and procedure (AHCPR Publication No. 93-0043). Rockville, MD: Public Health Service, Division of Provider Studies Research Note 17, Agency for Health Care Policy and Research.
47. Barendregt JJ (2010) The effect size in uncertainty analysis. *Value in Health* 13: 388-391.
48. Walsh BT, Seidman SN, Sysko R, Gould M (2002) Placebo response in studies of major depression: variable, substantial, and growing. *Jama* 287: 1840-1847.