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When is Pharmacogenetic Testing for Antidepressant Response Ready for the Clinic? A Cost-effectiveness Analysis Based on Data from the STAR*D Study

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Abstract

The potential of personalized medicine to transform the treatment of mood disorders has been widely touted in psychiatry, but has not been quantified. We estimated the costs and benefits of a putative pharmacogenetic test for antidepressant response in the treatment of major depressive disorder (MDD) from the societal perspective. Specifically, we performed cost-effectiveness analyses using state-transition probability models incorporating probabilities from the multicenter STAR*D effectiveness study of MDD. Costs and quality-adjusted life years were compared for sequential antidepressant trials, with or without guidance from a pharmacogenetic test for differential response to selective serotonin reuptake inhibitors (SSRIs). Likely SSRI responders received an SSRI, while likely nonresponders received the norepinephrine/dopamine reuptake inhibitor bupropion. For a 40-year-old with major depressive disorder, applying the pharmacogenetic test and using the non-SSRI bupropion for those at higher risk for nonresponse cost \$93,520 per additional quality-adjusted life-year (QALY) compared with treating all patients

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with an SSRI first and switching sequentially in the case of nonremission. Cost/QALY dropped below \$50,000 for tests with remission rate ratios as low as 1.5, corresponding to odds ratios ~1.8–2.0. Tests for differential antidepressant response could thus become cost-effective under certain circumstances. These circumstances, particularly availability of alternative treatment strategies and test effect sizes, can be estimated and should be considered before these tests are broadly applied in clinical settings.

Keywords

pharmacogenetics; major depressive disorder; cost-effectiveness; serotonin

Introduction

Multiple antidepressant medications have demonstrated efficacy for the treatment of major depressive disorder. However, prospective comparisons and metaanalyses suggest little difference in efficacy between them. At the same time, many patients do not reach remission with initial antidepressant treatment, with consequences including greater functional impairment, greater likelihood of discontinuing treatment prematurely, and substantially increased medical costs associated with more chronic illness. It has been suggested that, by allowing patients to be matched to the treatment likely to be most effective for them, pharmacogenetic testing will provide an opportunity to improve depression treatment outcomes.

Recent studies have suggested that common genetic variations are associated with antidepressant response (Kim *et al.*, 2006; McMahon *et al.*, 2006; Perlis *et al.*, 2008). Many of these results do not consistently replicate, do not address specificity of effect, or do not allow the estimation of the tests' performance in a general clinical population. Still, with larger clinical cohorts, these limitations are being overcome and the development of pharmacogenetic predictors of treatment response has become an active area of investigation.

Surprisingly, the question of when such testing will be suitable for clinical application, commonly raised by clinicians, has received minimal attention in psychiatry (Perlis *et al.*, 2005). Nonetheless, at least two psychiatric pharmacogenetic tests are now commercially available, with others in development.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which examined prospective outcomes in a very large cohort of patients receiving sequential antidepressant trials in a 'real-world' design, offers a unique opportunity to address the question of cost-effectiveness directly (Rush *et al.*, 2004). We utilized clinical and genetic data from STAR*D to estimate the cost-effectiveness of a recently-reported pharmacogenetic test for antidepressant response which was replicated using a split-sample design (McMahon *et al.*, 2006). Beyond examining the potential utility of that test as a 'base case', we developed a general-purpose model which allows the utility of any similar test to be estimated.

Methods

We modeled a population of individuals in a current episode of major depressive disorder, using a 3-year time horizon and societal perspective – that is, examining outcomes over 3 years from the perspective of the costs and health benefits to society. We incorporated data from the clinical literature in a model to estimate the outcome of alternative diagnostic and treatment strategies for a typical patient beginning outpatient treatment for MDD (see Figure 1). The treatment algorithm was based upon the ‘switch’ arms of the STAR*D study, with each treatment period lasting up to 12 weeks. Individuals are treated first with the SSRI citalopram. Those who fail to remit are then switched to bupropion, followed by nortriptyline, followed by the combination of venlafaxine and mirtazapine.

We modeled the implementation of the test for SSRI responsiveness, either prior to any treatment (‘test-first’), or following an initial treatment failure (‘test-second’), compared to the ‘no-test’ condition (Figure 1). In the ‘test-first’ condition, those with a test result indicating greater likelihood of SSRI response are triaged to an SSRI, while those with a lesser likelihood are triaged to bupropion. In the ‘test-second’ condition, those who fail an initial SSRI receive either a second SSRI or bupropion, based upon test results. As outcomes with the atypical antidepressant bupropion or the SSRI sertraline as next-step treatments were similar in STAR*D (Rush *et al.*, 2006b), we also varied the treatment strategies, allowing individuals to receive SSRI or bupropion as first- or second-line treatment. For purposes of comparison, we also examined a no-test, bupropion-first/citalopram-second strategy, to confirm that the test’s potential benefit did not simply derive from shifting patients to a more effective and lower cost strategy.

We developed a state-transition model of transition probabilities in which patients could occupy distinct health states, including depressed (on or off treatment) and well (on or off treatment) (Simon *et al.*, 2006). (For a review of the application of state-transition models in cost-effectiveness research in a related field, see Hsieh (Hsieh and Meng, 2007)). We used a cohort simulation to track transitions between states representing the expected effects among patients of the alternate strategies (Supplemental Figure 1), with a cycle-length of 3 months, corresponding to the duration of each treatment level in STAR*D. In other words, every 3 months, individuals can transition from one state to another. Models were constructed using the TreeAge Pro 2007 decision analysis program (TreeAge Software; Williamstown, MA).

Transition Probabilities (Table 1)

For each state in the state-transition model, there is an associated mortality rate describing probability of death in a given cycle. For depressed patients, this rate is calculated by adding the rate of suicide among depressed patients (O’Carroll *et al.*, 1996) to age-adjusted all-cause mortality rates from U.S. life tables (Statistics, 1998). For remitted patients, this is equal to the age-adjusted all-cause mortality rate. For sensitivity analyses, we used upper and lower bounds of the 95% confidence intervals around estimates of rates of death by suicide.

Probabilities of remission, discontinuation, and recurrence were drawn directly from those reported in STAR*D for each treatment level (Rush *et al.*, 2006a). Because STAR*D and prior metaanalysis (Salloum *et al.*, 2005) did not identify significant differences in remission

between SSRI and bupropion, values for bupropion and SSRI were set to be equal. Probabilities of recurrence following remission for treated and untreated patients utilized data from a systematic review(Gijsman *et al.*, 2004), with ranges incorporating additional long-term studies(Maj *et al.*, 1992; McGrath *et al.*, 2000).

Utilities (Health Effects)

Rather than simply considering whether subjects are alive or dead at each time point, the use of weights or utilities allows models to consider that different mood states may be associated with different quality of life (QOL). QOL weights for each mood and treatment state were drawn from the published literature, and can range from 0–1, with 1 representing ‘perfect’ quality of life. Remitted depression was assigned a utility of 0.88 based on values reported in studies assessing this health state directly using standard gamble and time-trade-off techniques(Bennett *et al.*, 2000; Revicki *et al.*, 1995; Revicki and Wood, 1998). Remitted depression without prophylaxis received utilities of 0.86 to 0.895. These values are generally consistent with the utilities reported for 40 year-olds in the Beaver Dam Health Outcomes Study(Fryback *et al.*, 1993) and in more recent studies(Fryback *et al.*, 2007; Sullivan *et al.*, 2005). Untreated depression was assigned a utility of 0.63, which was varied from 0.35 to 0.65 in sensitivity analyses(Revicki *et al.*, 1995; Revicki and Wood, 1998).Utilities reported for depression vary widely from 0.09 for severe, untreated depression to 0.75 for mild depression(Schaffer *et al.*, 2002); the base case was selected conservatively to reflect the prevalence of mild depression in outpatient populations, as well as so-called ‘partial responders’ who improve with treatment but do not remit. Treatment was assigned a disutility of 0.04 in our base case to reflect side effects associated with treatment, varied from a disutility of 0.06 (adverse effects – that is, worse quality of life among individuals experiencing adverse effects and no symptomatic change) to a utility of 0.22 (partial symptom improvement without full remission) in sensitivity analyses.

Costs

The following direct medical costs were included in the base case model: outpatient treatment (medication management) visits, hospitalization for severe depression, and antidepressant medications. Direct costs due to suicide were not included to avoid double-counting, as hospitalization rates already include hospitalizations for suicide. All costs were inflated to 2006 U.S. dollars using the medical care component of the Consumer Price Index (CPI-M)(Gold *et al.*, 1996). Drug costs were calculated from average wholesale generic price for the minimum number of pills necessary for median doses drawn from STAR*D.

As recommended by the Panel on Cost-effectiveness in Health and Medicine(Weinstein *et al.*, 1996), indirect costs such as those related to lost productivity and career opportunities were not included in the analysis. Such disease effects are likely to be captured in the utility weights assigned by patients to health states such as depression, and would therefore be double-counted if included as costs as well.

Pharmacogenetic testing parameters

While a number of pharmacogenetic tests are under active development, we focused on a single nucleotide polymorphism (SNP) in the serotonin 2A receptor (*HTR2A*) gene, which

was associated with citalopram response in the largest antidepressant pharmacogenetic study to date and replicated in a split-sample design (McMahon *et al.*, 2006). That publication did not report effect size for association with remission, and utilized a definition of remission in which individuals with intermediate response phenotypes (i.e., significant improvement without remission) were omitted. We therefore obtained primary genotypic data from that study and calculated pertinent test parameters, including probability of a positive test in a mixed-ethnicity cohort (56.8%) and remission rate ratio (1.28; 95% CI, 1.13 to 1.42) for those with and without at least one copy of the ‘risk’ allele at rs7997012 in *HTR2A*. As the true mechanism of effect for this variation is not known, we assumed a dominant model of effect because it demonstrated stronger association than under a recessive model (Perlis RH, unpublished). For one-way sensitivity analysis, we assumed a range of probabilities of a positive test between 0.05 and 0.95. As the overall remission rate in the STAR*D clinical cohort was somewhat less than that observed in the genetic cohort (McMahon *et al.*, 2006), we used weighted averages to recalculate remission rates assuming overall remission rates (36.8% for level 1 and 26.6% for level 2) equivalent to that in the clinical rather than genetic cohort. Of note, as the error rates with modern genotyping techniques are <<1%, and the reported test performance already accounts for such methodologic errors, we did not further correct for this source of error. For the one-way sensitivity analyses, as a primary purpose of this model was to examine the role of test parameters in pharmacogenetic test performance, we examined the effect of remission rate ratios ranging from 1 (i.e., no effect) to 2 (doubling of remission rate), corresponding to odds ratios for remission between 1 and 2.9 under our base assumptions for remission probability and allele frequencies. We considered effects in terms of remission rate ratios because this value is easily calculated from results in clinical trials and is not dependent on allele frequency (or probability of a positive test).

Discounting

We discounted all costs and health effects at an annual rate of 3% for the base case, with sensitivity analyses performed between 0% and 5%. This standard practice in cost-effectiveness analysis sets current costs as being worth more than those occurring in the future, reflecting the opportunity cost of spending money now (rather than, for example, investing it elsewhere) (Weinstein *et al.*, 1996).

RESULTS

Base-Case Analysis

For a 40-year-old with MDD, the SSRI as first- and second-line strategy was both cheaper and more effective than all other no-test conditions (Table 2). This finding was driven by the lower cost and lower treatment discontinuation rate associated with SSRI treatment compared to bupropion treatment. Compared to this strategy of treating all patients with an SSRI as first and second line therapy, the strategy of testing patients first and initiating those testing negative on bupropion cost an additional \$505.50 per patient but provided an additional 0.0054 quality-adjusted life years, yielding an incremental cost-effectiveness ratio (ICER) of \$93,520 (Table 2). ICER refers to the marginal (increase in) cost divided by the marginal (increase in) effectiveness, compared to the next most costly option – how much additional cost would be required for each 1-year increase in quality-adjusted life years. The

strategy of testing following an initial treatment failure was eliminated by extended dominance: relative to the common alternative of no testing, the strategy of testing patients first had a lower ICER, providing better value per dollar spent. (This is an example of extended dominance because testing first is more costly than testing following a treatment failure. If it were less costly, testing following a treatment failure would be eliminated through simple dominance as a more costly and *less* effective strategy. For additional examples, see (Center).)

Sensitivity Analyses

In one-way sensitivity analyses, we examined the impact of varying individual model parameters bearing on costs, probabilities, and utility of mood and treatment states. In most one-way sensitivity analyses, the incremental cost-effectiveness ratio for testing fell in the \$80,000 – \$100,000/QALY range. As expected, the cost of the test itself had a large effect on cost-effectiveness; as test cost varied from \$100 to \$1000, ICER ranged from \$19,152 to \$186,029. When test cost was set to \$0, the least costly strategy remains 2 SSRI trials, without testing. The other non-dominated strategy is the ‘test-first’ approach, which costs an additional \$5.50 and adds 0.0054 QALYs for an ICER of \$1,010. Costs of medication management visits, hospitalizations, and pharmacotherapies in general did not meaningfully impact ICER. In the latter case, this lack of difference is primarily attributable to the availability of generic preparations for the primary treatment options. The comparative cost of bupropion versus citalopram did impact which treatment-first option was favored, but with little meaningful effect on the ICER of testing.

We next examined the effects of varying test parameters or clinical cohorts. When we varied the response risk ratio over its 95% confidence interval (1.13 to 1.42), the ICER for testing decreased from \$218,000 to \$59,000 per QALY. We also considered scenarios where the genotype-specific remission rates are the same as in the base case, but the allele frequency is different. This circumstance might arise, for example, if a test identified in one ethnic group is applied in another ethnic group. In this case, the test's cost-effectiveness is greatest as the probability of a positive test approaches ~52%, the point at which the effectiveness of citalopram-first and bupropion-first strategies are equivalent. The cost/QALY is less than \$100,000 for probability of a positive test between 36% and 59%. When the prevalence of a positive result is either very high or very low, the choice of initial treatment strategy is more clear-cut and testing provides relatively little improvement in overall remission rates. At prevalences of 5 or 95%, the ICER of testing exceeds \$750,000/QALY.

We also explored the circumstances under which a different genetic test predicting SSRI response might be cost-effective. To do this, we held the overall level 1 and level 2 SSRI and bupropion response rates constant at 36.8% and 26.6% but varied the strength of the genotype / SSRI response association and the prevalence of the different genotypes in a 2-way analysis (that is, an analysis showing the effects of varying both parameters simultaneously) (Supplemental Figure 1). The benefit of genotyping is greatest when the prevalence of the two genotypes is approximately equal and when the absolute difference in response rates between the test+ and test- groups is the greatest. Under the base case assumptions, at a 'willingness to pay' of \$50,000/QALY, the testing strategy can be cost-

effective for ratios of remission between test+ and test- subjects as low as 1.5, provided the probability of a positive test is around 50%; this corresponds to an odds ratio of ~1.9.

For the primary analyses, efficacy of bupropion and SSRI were constrained to be the same as initial treatment, consistent with metaanalysis which fail to find significant efficacy differences between these treatments as first-line antidepressant options (Salloum *et al.*, 2005). In sensitivity analysis, their efficacy was allowed to vary independently. As expected, this variation primarily impacts the relative cost-effectiveness of a bupropion-first versus SSRI-first strategy. However, in the extreme case where SSRI treatment is modeled as being substantially more efficacious, the benefit of bupropion treatment for test- subjects is reduced and therefore the benefit of testing to identify these subjects is also reduced. When the level 1 bupropion remission rate was reduced to 35.3%, testing (which triages test(-) patients to bupropion) became less effective and the ICER for this strategy increased to \$145,000/QALY. Parameters of antidepressant treatment response otherwise had little impact on the model.

Finally, we varied the utility of mood states. As expected, when the disutility of depression increased (i.e., the discomfort of remaining depressed is considered to be greater), the value of testing increased, and vice versa. Notably, reducing the utility of untreated depression to 0.35 reduced the ICER to \$54,128/QALY with base case assumptions, suggesting that testing may be more cost-effective in a more severely depressed population. In 3-way sensitivity analysis examining prevalence of a positive test, remission rate ratio for positive versus negative test, and utility of the depressed state (Supplemental Figure 2), for a depression utility of 0.35, testing ICER is below \$50K if the likelihood of a positive test is ~50% and remission rate ratio (for test+ versus test-) is greater than 1.3.

DISCUSSION

Most genetic association studies conclude with a statement about how positive findings could be used to improve clinical outcomes, though cost-effectiveness of genetic tests has received remarkably little attention in psychiatry (Perlis *et al.*, 2005). With our base-case assumptions, utilizing a large-scale effectiveness study intended to mimic clinical practice, the incremental cost-effectiveness of a putative pharmacogenetic test is \$93,520/QALY relative to the next best strategy of using an SSRI as 1st and 2nd level treatment for all subjects. While there is no accepted threshold below which interventions should be funded, one widely-cited number, based on the cost-effectiveness of dialysis in chronic renal failure patients covered by Medicare, is \$50,000/QALY (Winkelmayer *et al.*, 2002). It has been noted that few interventions with cost-effectiveness ratios exceeding \$100,000/QALY receive funding (Laupacis *et al.*, 1992). Within psychiatry, a recent cost-effectiveness analysis suggested that a simple depression care program for employees led to an incremental cost-effectiveness ratio of \$20,000 per QALY (Simon *et al.*, 2006), consistent with other primary care quality-improvement programs yielding ratios less than \$50,000 (Simon *et al.*, 2001). Relative to these numbers, the ICER for the genetic test, with our base-case assumptions, would not be considered cost-effective. Of course, as genotyping rapidly becomes a commodity, the cost of testing would likely fall substantially. In the extreme, where testing is free, the cost/QALY is ~\$1,000, well within the range considered

to be cost-effective. Notably, the magnitude of difference between QALYs resulting from the strategies examined is modest, and below the threshold suggested by some authors to represent clinically meaningful differences (Kaplan *et al.*, 1993). On the other hand, given the prevalence and costliness of MDD, even modest differences in outcomes bear consideration by policymakers. In the subset of patients whose treatment is changed by testing, the initial response rate is increased by 5%. With a 0.25 QALY difference between a year of depression and a year of remission, this is arguably a clinically meaningful improvement.

With base-case assumptions, we found that a pharmacogenetic test for antidepressant response could only be considered cost-effective for tests with odds ratios ≥ 1.5 . Multiple potential strategies could be applied by clinical researchers to identify such cost-effective tests. First, incorporating multiple informative loci will likely be necessary to achieve this threshold. Recent genomewide association studies of antidepressant response indicate that individual loci are likely to exert only modest effects (Hamilton, 2007), so any pharmacogenetic test would likely need to incorporate multiple informative loci to achieve an adequate OR. Second, more effective tests could incorporate other putative clinical predictors such as those identified in the STAR*D study (Trivedi *et al.*, 2006). Addition of clinical predictors would simply be reflected in better test performance (i.e., greater effect sizes).

An alternate strategy would rely on tests informative about multiple treatment strategies: rather than focusing solely on SSRIs, a test which was also informative about common alternative strategies could be more cost-effective. To date, few antidepressant pharmacogenetic studies include such non-SSRI comparators and describe specific predictors for the alternate strategy. Similarly, the incorporation of predictors of adverse effects could offer another strategy for designing cost-effective tests. While modern antidepressants are quite safe and generally well-tolerated, many patients do discontinue treatment prematurely. A number of recent reports suggest that it may be possible to predict specific adverse effects (Laje *et al.*, 2007; Perlis *et al.*, 2003; Perlis *et al.*, 2007).

Our results underscore the importance of understanding pharmacogenetic test performance in the population in which it is being applied. While this is true in general for any test, it becomes particularly important given the known wide variation in allele frequencies between racial groups (2003). Apart from individual studies in Southeast Asian or Latino populations (Kim *et al.*, 2006; Wong *et al.*, 2006), the vast majority of association studies for antidepressant responsiveness focus on Caucasians. Notably, the 'beneficial' allele frequency for the test considered here is less prevalent among African-Americans (McMahon *et al.*, 2006). Our results demonstrate that the cost-effectiveness of such tests is critically dependent upon the effect size, and test probabilities, in the target population, suggesting that more representative cohorts will be required to determine the true utility of pharmacogenetic tests.

We note several caveats in interpreting our base-case results. Most importantly, our estimates rely on numerous assumptions about model parameters which are imprecise and likely to vary across clinical settings. However, a strength of this study is that it closely

follows results of one of the largest antidepressant-effectiveness studies completed to date. Not only was that study designed to mirror clinical practice, but it took place in both primary care and specialty psychiatric clinics, suggesting our results can be informative about 'real-world' treatment of MDD (Rush *et al.*, 2004). Many of the parameters not drawn from STAR*D were previously utilized in a cost-effectiveness model of an employer-based depression intervention (Wang *et al.*, 2006) which was later validated in a prospective study (Wang *et al.*, 2007). This model can thus be understood in terms of 'how might STAR*D outcomes have differed if initial treatment assignment was determined by a genetic test', assuming a standard set of next-step interventions. Of note, our results likely underestimate the 'true' cost-effectiveness of the intervention because, as with most such analyses, we do not include the costs to caregivers or other family members (Weinstein *et al.*, 1996).

We emphasize that, although we utilized an existing genetic finding as our base case, the general model can be applied to any pharmacogenetic test of antidepressant response. The code for this model is available at [website]; simply substituting the appropriate test parameters allows cost-effectiveness of that test to be estimated. The first marketed pharmacogenetic test to be advocated for antidepressant prescribing is actually one which examines cytochrome p450 variation (Somanath *et al.*, 2002), though it has previously been suggested that such a test is likely to have little impact on general antidepressant prescribing (Perlis, 2007). Similarly, a serotonin transporter promoter insertion/deletion polymorphism is the genetic variation most often associated with antidepressant responsiveness, albeit in small cohorts (Serretti *et al.*, 2006). However, the specificity of its effect is not well characterized, and the largest cohort to date did not detect an association with treatment response, though incorporating an additional polymorphism did identify some association with overall citalopram tolerability (Hu *et al.*, 2007). Therefore, we focused on the HTR2A variation because it was replicated in a split-sample design and exerts a well-defined impact on response. We note that, even if it represents a true association, its effect size is almost certainly less than that estimated here, based upon the phenomenon of the 'winner's curse', or regression to the mean. Future pharmacogenetic tests will almost certainly incorporate multiple markers drawn from genomewide association studies, but the basic principles of our model can be applied regardless of the type or scale of the genetic test.

We also made the simplifying assumption that the HTR2A-based test is not informative about response to other (non-SSRI) treatments. While this appears to be the case in STAR*D (Laje and McMahon, unpublished data) and other cohorts (Perlis, unpublished data), these effects have not been fully characterized. In general, this assumption would yield an optimistic estimate in the base case, and underscores the need to understand not simply predictors of nonresponse to a given treatment, but the specificity of such predictors, prior to their clinical application. That is, it will be important to characterize not only predictors of differential response to a single treatment, but also the effects of such predictors on response to alternative treatment strategies.

Third, we included two primary types of states in our state-transition model, 'depressed' and 'well', either on- or off-antidepressant. The gradation of treatment responses in depression is

well-known - based upon STAR*D, roughly one-third of patients improve with treatment but do not reach symptomatic remission(Trivedi *et al.*, 2006). The effects of including individuals who improve but do not remit in treatment among the 'depressed' state would be to dilute or decrease the disutility of depression, rendering our model overly conservative. On the other hand, the significant impact of continued depressive symptoms even among those who improve with treatment is well-documented(Wells *et al.*, 2007).

A further simplification was the requirement that nonremitters have their treatment switched, rather than augmented (Fava, 2001). In routine outpatient settings, augmentation is generally a much less common strategy, particularly in primary care settings. A survey of clinicians suggested that substantial variation exists in their preference for treatment sequence(Petersen *et al.*, 2002), perhaps because other prior to STAR*D there was little controlled data bearing on the efficacy of augmentation in general(Fava, 2001).

Notwithstanding these caveats, our results suggest a means for evaluating future pharmacogenetic tests in psychiatry. To our knowledge, only one previous report addressed the value of such psychiatric tests in terms of cost-effectiveness; in that study, we found that a test for clozapine responsiveness could be cost-effective under certain conditions(Perlis *et al.*, 2005). As with pharmacotherapy, determining the true cost-effectiveness of a diagnostic intervention will require either large randomized prospective studies or retrospective assessment of large clinical population. With the substantial public interest in personalized medicine, pressure will be great to quickly translate tests to clinical practice. Our results suggest that the cost-effectiveness of these tests can be modeled in a straightforward fashion, allowing necessary test parameters and integration with treatment algorithms to be carefully considered prior to implementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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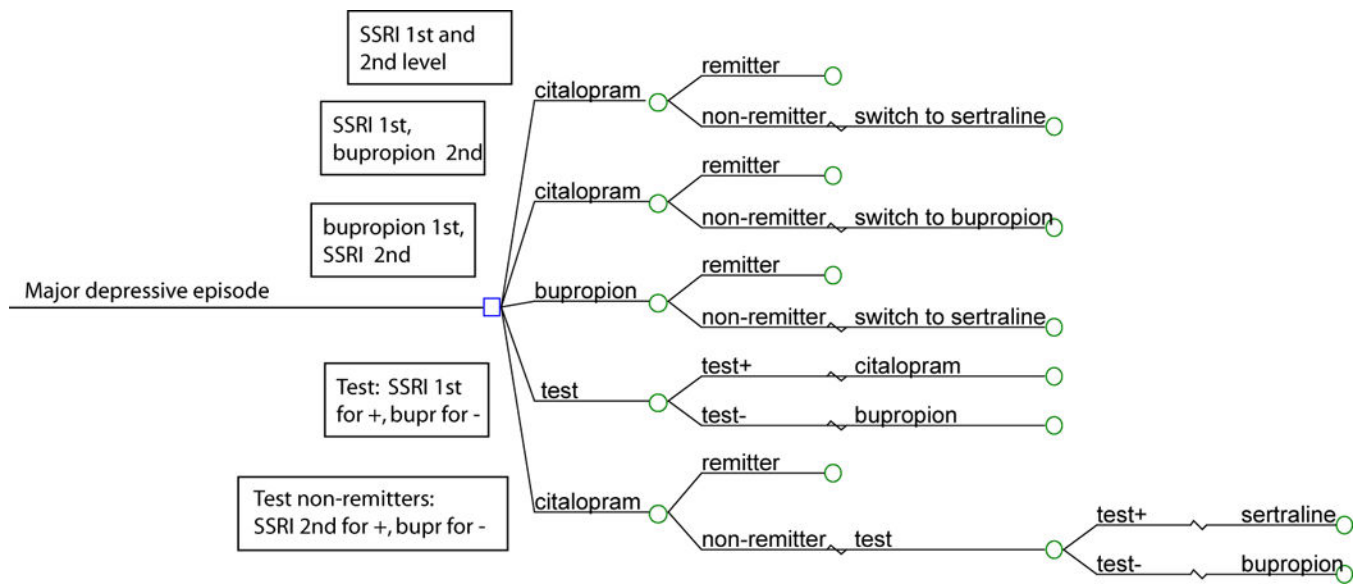
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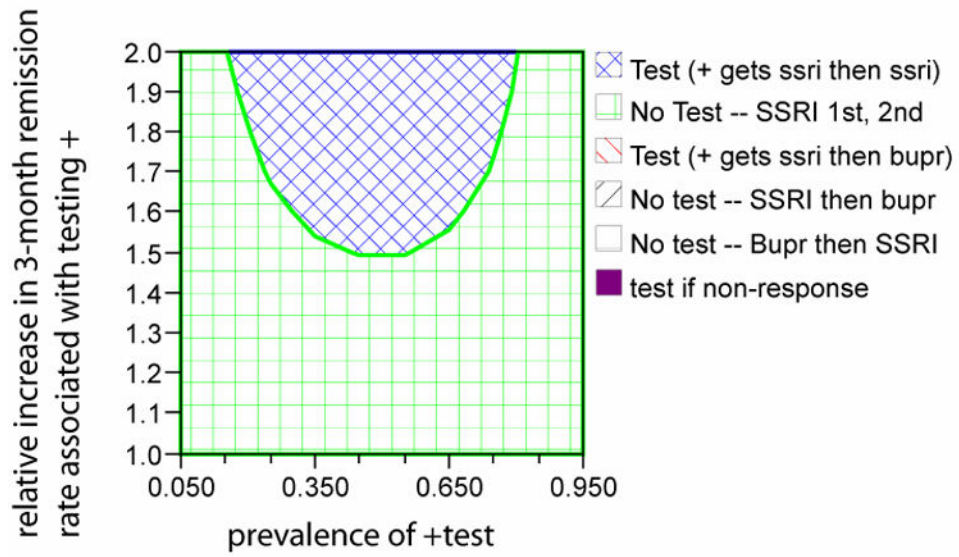
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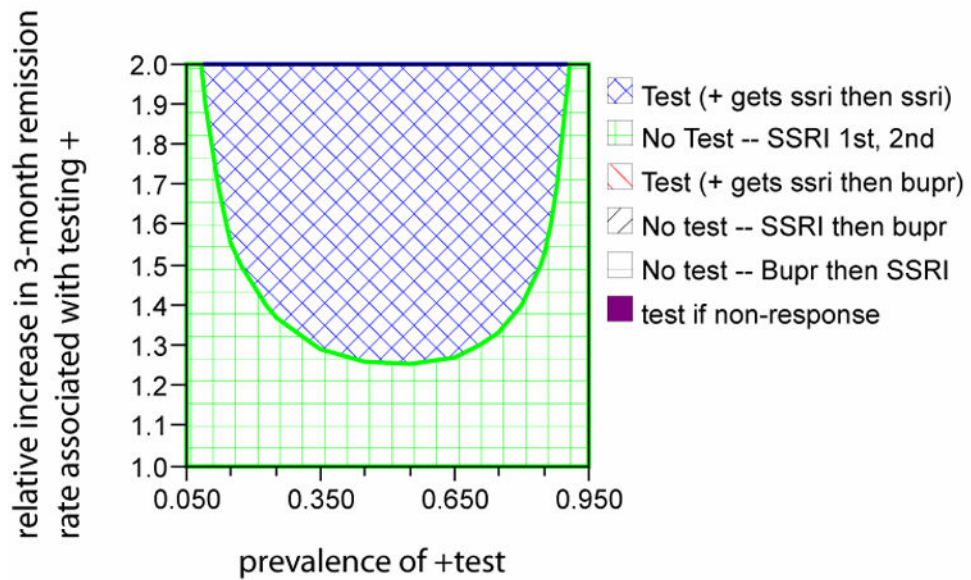
Decision analytic model for antidepressant treatment of major depressive disorder

Figure 1 presents a schematic of the decision model used in this analysis. All patients begin in a major depressive episode. They may receive initial treatment with citalopram or bupropion, with or without treatment assignment based upon the result of the genetic test. Individuals who fail to respond to initial treatment may receive sertraline or bupropion.

A: If 1 QALY is valued at \$50,000



B: If 1 QALY is valued at \$100,000



Two-way sensitivity analysis of the prevalence of a positive test result and the strength of association between test result and SSRI response

2-way sensitivity analysis of the prevalence of a positive test result and the strength of association between test result and SSRI response. The top panel assumes a willingness to pay of \$50,000 per quality-adjusted life year (QALY). The bottom panel increases this value to \$100,000 per QALY. For each value of the prevalence of test+ and test effect size, an optimal strategy can be found by identifying the corresponding region in the graph and

matching the color of that region to the color-coded key. SSRI, selective serotonin reuptake inhibitor; bupr, bupropion

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Table 1

Parameters used in the base-case and sensitivity analyses

Parameter	Estimate	Range*	Source
Patient age	40.8	27.8–53.8	STAR*D mean/SD(Trivedi <i>et al.</i> , 2006)
Probabilities (3-month)			
Background mortality rate	0.000538	n/a	(Arias, 2004)
Suicide rate for depressed	0.0009	0.000275–0.0055	(O'Carroll <i>et al.</i> , 1996)
Probability of remitting on no treatment	12%	0 - minimum of other treatments in model	(Research, 1993)
Probability of relapse on no treatment	12.4%	4.8 – 27.3%	(Gijsman <i>et al.</i> , 2004; Maj <i>et al.</i> , 1992) (maximum from (McGrath <i>et al.</i> , 2000))
Probability of re-starting treatment if depressed (and quit previously)	16.6%	0 – 25%	(Kessler <i>et al.</i> , 2003)
<i>Treatment efficacy and tolerability</i>			
Probability of remission on SSRI (population averages)			(Research, 1993; Rush <i>et al.</i> , 2006a)
If 1 st level (citalopram)	36.8%	35.3 – 38.4%	(Rush <i>et al.</i> , 2006a)
If 2 nd level (sertraline)	26.6%	21.3 – 32.4%	(Rush <i>et al.</i> , 2006a)
Probability of remission on bupropion			
If 1 st level	36.8%	35.3 – 38.4%	(Rush <i>et al.</i> , 2006a)
If 2 nd level	26.6%	21.3 – 32.4%	(Rush <i>et al.</i> , 2006a)
Probability of remission on nortriptyline	12.4%	8.0 – 20.2%	(Rush <i>et al.</i> , 2006a)
Probability of remission on venlafaxine + mirtzapine	16.0%	8.3 – 28.5%	(Rush <i>et al.</i> , 2006a)
Probability of relapse on treatment	4.8%	0 – 14.2%	(Gijsman <i>et al.</i> , 2004)
Probability of discontinuing treatment			(Rush <i>et al.</i> , 2006a)
SSRI	21.0%	16.3 – 26.6%	
Bupropion	27.2%	21.9 – 33.2%	
Nortriptyline	32.8%	24.9 – 41.7%	
Venlafaxine/mirtzapine	20.0%	11.2 – 33.0%	
Probability of hospitalization			
On treatment	0.9%	0.1 – 2.0%	(Valenstein <i>et al.</i> , 2001)
Not on treatment	1.4%	0.1 – 2.0%	(Valenstein <i>et al.</i> , 2001)
<i>Test parameters</i>			
Probability of testing +	56.8%	5 – 95%	(McMahon <i>et al.</i> , 2006) and Perlis RH, unpublished
Relative risk of recovery (test+ vs –)	1.28	(calculated)	(McMahon <i>et al.</i> , 2006) and Perlis RH, unpublished
Implied genotype-specific 1 st level recovery rates	31.4 for test–, 40.1 for test+	(calculated)	(calculated)
Implied genotype-specific 2 nd level recovery rates	22.8 for test–, 29.2 for test+	(calculated)	(calculated)

Parameter	Estimate	Range*	Source
Utilities			
<i>Recovered</i>			
Not on treatment	0.88	0.80 – 1.0	(Bennett <i>et al.</i> , 2000; Revicki <i>et al.</i> , 1995; Revicki and Wood, 1998)
Disutility of treatment (any)	0.04	0 – 0.06	(Revicki <i>et al.</i> , 1995; Revicki and Wood, 1998)
<i>Depressed</i>			
Not on treatment	0.63	0.35 – 0.65	(Revicki <i>et al.</i> , 1995; Revicki and Wood, 1998; Schaffer <i>et al.</i> , 2002)
Disutility on treatment (any)	0.04	–0.22 – 0.06 (adverse effects to partial symptom relief)	(Revicki <i>et al.</i> , 1995; Revicki and Wood, 1998)
Costs			
<i>Drug costs (3 month)</i>			
SSRI (citalopram)	\$251	\$188 – \$314	(Anonymous, 2006) (Based on formulations closest in size to median dose)
Bupropion	\$442	\$332 – \$553	
Nortriptyline	\$248	\$186 – \$310	
Venlafaxine + mirtazapine	\$840	\$630 – \$1,050	
Medication management visit costs	\$191.41	\$144 – \$239	2 visits per cycle for 70% receiving care from PCP + 4 visits per cycle from 30% seeing psychiatrist. Utilization was from (Grembowski <i>et al.</i> , 2002); costs from Medicare fee schedule (Services, 2004).
Genotyping test cost	\$500	\$0 – \$1,000	(Staples, 2007)
Cost of hospitalizations due to depression	\$6889 per hospitalization.	\$5,167 – \$8,622	(Quality)

* Except where specified, parameter ranges utilize 95% confidence intervals calculated from, or cited in, primary sources; for costs, parameter ranges utilize +/-25% of base case value.

Table 2

Results of cost-effectiveness analysis

Strategy	Base Case Analysis			Incremental Values		
	Cost	Effectiveness	Cost	Effectiveness	Cost	Effectiveness ratio (ICER)
No Test -- SSRI as level 1 and 2	\$3,380	2.119				
No Test -- SSRI then bupropion	\$3,477	2.118				Dominated*
No test -- Bupropion then SSRI	\$3,481	2.117				Dominated
Test if non-response	\$3,765	2.121				Extended dominance*
Test (+ gets ssri then ssri)	\$3,890	2.124	\$510.00	0.0054		\$93,520
Test (+ gets ssri then bupr)	\$3,960	2.121				Dominated

* Strategies are dominated if there is a competing strategy that is more effective and less costly. They are subject to extended dominance, sometimes referred to as weak dominance, if its incremental cost-effectiveness ratio is greater than, and its effectiveness less than, a competing strategy. For example, here 'test if non-response' is eliminated through extended dominance because its ICER is greater than the 'test, give test positive subjects ssri followed by another ssri trial', and its effectiveness is less. (For further examples, see (Center)).

Incremental values here are presented for non-dominated strategies only and are relative to the preceding non-dominated strategy. SSRI, selective serotonin reuptake inhibitor; bupr, bupropion