



ORIGINAL INVESTIGATION

A model to incorporate genetic testing (5-HTTLPR) in pharmacological treatment of major depressive disorders

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Abstract

Objective. To evaluate the benefit of pharmacogenetics in antidepressant treatment. **Methods.** In a simulated trial 100,000 subjects in a current episode of major depressive disorder (MDD) received citalopram or bupropion based on the clinician's decision (algorithm A) or following indications from 5-HTTLPR genetic testing (algorithm B), which effect size of was estimated from a meta-analysis of pharmacogenetic trials. A and B were compared in a cost-utility analysis (12 weeks). Costs (international \$, 2010) were drawn from official sources. Treatment effects were expressed as quality-adjusted life weeks (QALWs). Outcome was incremental cost-effectiveness ratio (ICER). **Results.** Under base-case conditions, genetic test use was associated with increases in antidepressant response (0.062 QALWs) and tolerability (0.016 QALWs) but cost benefit was not acceptable (ICER = \$2,890; \$1,800–\$4,091). However, when the joint effect on antidepressant response and tolerability was analyzed in two recurrent episodes, ICER dropped to \$1,392 (\$837–\$1,982). Cost-effectiveness acceptability curve (CEAC) showed a >80% probability that ICER value fell below the commonly accepted 3 times Gross Domestic Product (GDP) threshold (World Health Organization) and therefore suggesting cost-effectiveness. **Conclusion.** Notwithstanding some caveats (exclusion of gene–gene and gene–environment interactions; simple 5-HTTLPR architecture), this simulation is favourable to incorporate pharmacogenetic test in antidepressant treatment.

Key words: Depression, antidepressants, pharmacogenetics, pharmacoeconomics, cost-benefit

Introduction

Major depressive disorder (MDD) is a prevalent psychiatric disorder worldwide (Lepine 2001), weighted by hundreds fold increased mortality from suicide (Moller 2003; Bradvik et al. 2008) and an impressive burden for society in terms of work disability (Ryt-sala et al. 2005; Adler et al. 2006; Bender and Farvolden 2008) and health expenditure (Birnbaum et al. 2009; Watkins et al. 2009). Moreover health-related quality of life (HRQoL) in major depression is inferior to the general population (Sapin et al. 2004; Aydemir et al. 2009) and comparable with the burden in severe physical disorders (Soeteman et al. 2005; Buist-Bouwman et al. 2006). Although novel antidepressant drugs have proven to be effective in reducing symptoms and improving HRQoL (Sarnes and Frankum 2004; Sullivan et al. 2004; Llorca and Fernandez 2007), approximately one-third of patients

with MDD fail to respond to a correctly delivered antidepressant treatment and only 20–30% achieve remission (Ferrier 1999). Antidepressant response is in part under genetic control as seen in randomized trials (Kim et al. 2006; Serretti et al. 2007a,b; Kato and Serretti 2010) and, to a lesser extent, in naturalistic studies (Laje et al. 2009; Villafuerte et al. 2009). Thus an emerging field of psychiatric research is pharmacogenetics. This approach holds promise to improve the outcome of major depression treatment by tailoring drug choice to individual's genetic makeup (Serretti et al. 2005). In other words, if drug 'X' was delivered to individuals with a favourable genetic profile, the number of responders would be increased. This hypothesis, although intriguing, is not supported by empirical data. However it is possible to simulate the use of a genetic test to select antidepressant treatment and to forecast outcome

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based on literature findings. Perlis et al. (2009) performed a cost-utility study based on data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Costs and quality-adjusted life years (QALYs) were compared for sequential antidepressant trials, with or without guidance from a pharmacogenetic test (5-HT_{2A} polymorphism) for differential response to selective serotonin reuptake inhibitors (SSRIs). In a simulated scenario, likely SSRI responders received an SSRI, likely nonresponders were prescribed the nor-epinephrine/dopamine reuptake inhibitor bupropion. Economic evaluation was based on US costs. Time-horizon for cost-effectiveness analysis was three years. Authors concluded that a benefit was present but only under certain circumstances. Thanks to this study, we gained more information about genetic testing applicability to antidepressant treatment. Nevertheless some characteristics of its design are difficult to evaluate for real world settings (see Discussion). We applied a similar model, however modified in some aspects, to Italian mental health setting. In Italy health services are delivered to the entire population subdivided into catchment areas by local providers (Aziende Sanitarie Locali) that are funded by regional governments. Secondary care for mental disorders is provided at outpatient level in community-based centres under control of the Aziende Sanitarie Locali. Inpatient treatment is delivered in general hospital psychiatric wards (Servizi Psichiatrici di Diagnosi e Cura, SPDC). Secondary hospitals are controlled by the Aziende Sanitarie Locali. Tertiary hospitals are independent public institutions. Since 1995 the Aziende Sanitarie Locali have reimbursed hospitals for cares provided to individual patients based on a diagnosis related group (DRG) system. As for the genetic part, we selected the Serotonin Transporter Gene Promoter Polymorphism (5-HTTLPR). A single marker could result in an easy algorithm to incorporate genetic data in antidepressant selection. Moreover, testing one SNP is less expensive than multiple gene tests. The 5-HTTLPR polymorphism was found to moderate response to SSRIs in a large number of studies since 1998 (Smeraldi et al. 1998). A meta-analysis of randomized trials confirmed this influence in Caucasian samples: individuals with one or two copies of the 5-HTTLPR long (l) allele were more likely to respond than subjects who were homozygous for the short (s) allele (Serretti et al. 2007a). A 5-HTTLPR modulation of antidepressant response was also shown in the STAR*D sample, although its effect was weaker (Mrazek et al. 2009). More recently it has emerged that the 5-HTTLPR polymorphism not only influences antidepressant response to SSRI drugs but also tolerability (Kato and Serretti 2010).

The unfavourable variant is still the short allele (Popp et al. 2006). Thus the same gene variant would allow to optimize clinical response as well as to minimize side-effect burden. The structure and function of the 5-HTTLPR is more complex. A SNP in the promoter region of the serotonin transporter gene (rs25531; A/G) transformed the 5-HTTLPR into a triallelic locus (Hu et al. 2006). The L_G and s alleles showed comparable levels of serotonin transporter expression, both of which were inferior to the L_A. This led to reconsider the role of the serotonin transporter gene. Thus, in STAR*D patients, the haplotype composed of the 5-HTTLPR and rs25531 loci was associated with remission under SSRI treatment (Mrazek et al. 2009). The L_A allele was also associated with a lesser side effect burden (Hu et al. 2007). This difference did not hold when the L allele was undifferentiated. Three rare 5-HTTLPR alleles were recently described. Two of these novel alleles (XL) are longer than the common 16-repeat long allele (17 and 18 repeats, respectively) and characterized by higher transcription levels. The third allele has 11 repeats and it is functionally comparable with the short-allele (S) (Ehli et al. 2011). We performed a simulated trial to ascertain the cost-utility of treating major depressive episode under guidance from 5-HTTLPR genetic testing. Time frame for analysis was 12 weeks. This horizon might better reflect real world situations and it was recommended to follow up antidepressant response in pharmacogenetic studies (Serretti et al. 2007b). Costs were determined from National Health System perspective. Our simulation had three goals: (1) to estimate theoretical gain in antidepressant response if genetic information was used to select the most appropriate antidepressant treatment (effect A); (2) to estimate reduction in side effect burden (effect B) due to pharmacogenetic approach and to pool effect A and effect B; (3) to ascertain benefits from pharmacogenetic approach for multiple episodes in recurrent MDD.

Patients and methods

The characteristics of this simulation are reported below.

Sample

A hypothetical cohort of Italian patients ($N = 100,000$) affected by MDD (Table I). These patients are all of Caucasian origin and similar to the STAR*D sample ($N = 3,671$) (Rush et al. 2006) as for demographic and clinical features. Severity of depressive symptoms is based on the Hamilton Rating Scale for Depression (HDRS17) (Hamilton

Table I. Characteristics of the cohort.

	Mean \pm SD	%
Age	40.8 \pm 13.0	
Women		0.64
Never married		0.29
Education years	13.4 \pm 3.2	
Unemployed		0.38
Recurrent MDD		0.76
Number of episodes	6.0 \pm 11.4	
Length of illness (years)	15.5 \pm 3.2	
Axis I comorbidity		0.35

The characteristics of this cohort are based on the STAR*D sample (N = 3,671) (Rush et al. 2006). However, we highlight a few differences: (1) all patients are of Caucasian origin; (2) depressive symptoms are moderate (HAMD 14–18) and severe (HAMD 19–22).

1967); symptom gradations is as proposed by the National Collaborating Centre for Mental Health (2005): no depression: 0–7; mild symptoms: 8–13; moderate symptoms: 14–18; severe symptoms: 19–22; very severe symptoms \geq 23. We assume that our patients have moderate or severe depression.

Decision-analytic model

A decision-analytic model is implemented to simulate pharmacological treatment of major depressive episode. We report basic assumptions in brief. The diagnosis of MDD, established by treating physicians, is confirmed by a checklist based on Diagnostic and Statistic Manual-IV-TR (DSM-IV-TR) criteria. Clinical information is collected within routine interviews in the first contact. Antidepressant treatment is the only treatment delivered. Each patient receives either citalopram or bupropion for the entire follow-up (12 weeks). Target dose is reached in 2 weeks and no further dose-adjustment is allowed. Treatment goal is remission (HAMD17 \leq 7). Citalopram is a pure serotonergic agent (Stahl and Muntner 1998). Response to citalopram is affected by genetic variations in the 5-HTTLPR polymorphism (Arias et al. 2003; Mrazek et al. 2009). Conversely the antidepressant effect of bupropion, a dopamine and norepinephrine reuptake inhibitor, is not likely to be affected by 5-HTTLPR genotypes. In fact the 5-HTTLPR polymorphism modulates response to SSRIs but not to other (e.g., noradrenergic) antidepressants (Pollock et al. 2000; Huezo-Diaz et al. 2009). Remission rates and delay in antidepressant response are similar for the two drugs (Papakostas et al. 2007, 2008) as well as general tolerability, although there might be differences in specific side-effects (Gartlehner et al. 2008). Two algorithms are alternatively used to simulate antidepressant choice:

Algorithm A. Each patient is assigned to receive either drug based on the clinician's decision and following an "as usual" procedure. Citalopram is first choice antidepressant. This is close to "real world" treatment conditions in Italy where SSRIs are the most prescribed drugs for depressive disorders (Poluzzi et al. 2004). Bupropion is selected as initial treatment if the patient is likely to be affected by SSRI-related side effects (e.g., sexual dysfunction) or he/she has previous non-response to SSRI treatment (Zetin et al. 2006; Bauer et al. 2008). In Italy bupropion has been licensed for major depression treatment since 2008. Its use as first line treatment is still uncommon and this may represent a limitation of our model.

Algorithm B. Patients are tested for the serotonin transporter 5-HTTLPR polymorphism before starting treatment. Genotyping is performed as described in a similar study (Smits et al. 2007), with some modifications, as follows: the FAM-labeled forward primer 5'-GGCGTTGCCGCTCTGAATGC-3' is used with the reverse primer 5'-GAGGGACT-GAGCTGGACAACCCAC-3'. Polymerase chain reaction (PCR) is carried out in 96-well microtiter-plates on a Biometra T3 thermocycler (M-Medical, Milan, Italy). Approximately 10–100 ng of genomic DNA in a 25- μ l reaction mixture containing 1 \times PCR buffer (Invitrogen Corporation, Milan, Italy), 0.2 mM deoxynucleotide triphosphate (dNTPs), 0.4 μ l of each primer, 0.75 mmol/l of magnesium chloride (MgCl₂), and 1 U of Taq DNA polymerase (Invitrogen Corporation). The cycling conditions are as follows: initial 3-min denaturation at 95°C; five cycles of denaturation at 94°C for 30 s, annealing at 65°C (touchdown, 0.3°C) for 1 min, and extension at 72°C for 1 min; 35 cycles of denaturation at 94°C for 30 s, annealing at 63°C for 1 min, extension at 72°C for 1 min; and a final extension for 10 min at 72°C. For each sample, PCR products are pooled (1 μ l each) and subsequently size-resolved on an ABI3100 genetic analyzer (Applied Biosystems, Foster City, CA). The peaks corresponding to the various alleles are identified using GeneScan Analysis software version 3.7 (www.appliedbiosystems.com). Antidepressant selection is determined by genetic test results, under the hypothesis of a dominant effect of the 5-HTTLPR l-allele (Serretti et al. 2007a). In detail, patients with at least one l-allele, likely responders to SSRI treatment, receive citalopram. Instead individuals who are homozygous for the short allele, less responsive to SSRI drugs, are treated with bupropion. Novel 5-HTTLPR alleles were not considered because they were analyzed in few studies or not previously analyzed.

State-transition model

Resource consumption and benefits are computed using a state-transition model. Briefly, patients are classified into a number of different health states, each associated with a certain cost and HRQoL. As time progresses in the model, each patient moves from one state to another according to a set of transition probabilities and in a defined interval called a cycle. The percentage of a hypothetical cohort in a state during a cycle is multiplied by the cost and HRQoL associated with that state, and these products are summed over all states and all cycles. We project that a patient is initially in acute depression, then he can remain in this state, move to remitted depression or drop out during a cycle lasting 12 weeks. In order to compute HRQoL and cost, we hypothesize that such transitions occur after 8 weeks. From this time to endpoint all patients remain in the same state. As noted above SSRI agents and bupropion have comparable effectiveness and tolerability profiles (Thase et al. 2005; Gartlehner et al. 2008; Papakostas et al. 2008), therefore we project the same remission and dropout rates for the two antidepressants. To simplify estimates, we do not consider mortality. Indeed mortality from all causes is approximately 0.0001 annually in Italy (www.istat.it). Suicide rate in antidepressant trials is 0.15% (Khan et al. 2006).

Base-case parameters

Drugs and managed care. Daily doses of citalopram (range 20–60 mg; mean 41.8 ± 16.8 mg) and bupropion (range 100–300 mg; mean 282.7 ± 104.4 mg) are retrieved from the STAR*D sample (Rush et al. 2006). Managed care is similar to Italian practice. After a first assessment visit, a minority of patients are admitted to general hospital psychiatric wards. After a few weeks, they are discharged from hospital and followed as outpatients. A larger part of the cohort is treated in outpatient setting for the entire follow-up. Based on international sources, which apply to Italian context as well, estimated hospitalization rate is 12% (Banks et al. 1998; Sheehan et al. 2008). No differences in hospitalization rates are expected between patients treated with citalopram or bupropion (Sheehan et al. 2008) as well as between remitters and nonremitters. Length of hospital stay (LOS) is 21 ± 15 days (OECD 2009), without differences between remitters and nonremitters (Cheng et al. 2007). In fact in Italy psychiatric hospitalization is aimed at stabilizing the most critical patients; as soon as possible they are discharged and followed as outpatients until remission. Outpatient visits are held by physicians in community mental

health centers (www.who.int/choice/en/). Each visit lasts approximately 20 min. The frequency of visits, established according to published guidelines (APA 2000) and similar to Italian practice, ranges from once weekly in acute depression to once every two months in remitted patients. The frequency of visits is different in out- and inpatients. Outpatients are visited by a physician once weekly until remission (week 8) or until follow up end-point (week 12). In inpatients LOS is subtracted from the number of visits. Based on these assumptions, we summarize outpatient visits in remitters, non-remitters and dropout patients. Remitters have an average of eight visits if not hospitalized. Remitters who are hospitalized have only five visits. In non-remitters visits are 12 and nine in outpatients and inpatients, respectively. Dropout patients, including 16% with remission and 84% who do not remit (see attrition paragraph), have the same number of visits as remitters, but antidepressants are discontinued after 8 weeks.

Costs. Direct costs for treatment include costs for drug acquisition, genetic test as well as unit costs for outpatient visits and days spent in hospital. Information on drug prices is collected from the electronic version of the Italian national formulary *Prontuario Farmaceutico 2010* (www.prontuariofarmaceutico.it). The cost of genetic test is derived from the *Tarifario dei servizi resi a pagamento dall'Istituto Superiore di Sanità* (<http://www.iss.it>). Mental health care costs (hospitalization; outpatient visits) are estimated based on WHO-CHOICE methodology (<http://www.who.int/choice/en/>). Unit costs are specific to public hospitals, with occupancy rate of 80% and representing the hospitality component of hospital costs i.e. excluding drugs and diagnostic tests and including other costs such as personnel, capital and food costs. Inpatients are admitted to secondary or tertiary-level hospitals (<http://www.who.int/choice/en/>) after their first assessment visit as outpatients. Thus we use an average of the two costs. Post-discharge visits are held in outpatient centres. We analyzed unit cost per visit at health centres by 95% level of population coverage. Cost data are referred to 2010 and converted into international dollars using purchasing power parity (ppp) exchange rates. The ppp exchange rate for Italian currency unit is 0.86 (reference year 2010) Cost units for visits and days spent in hospital, available for year 2005, are inflated by 9.5% (1.9% annual inflation rate recorded in Italy in the period 2005–2010) (www.istat.it). As recommended in guidelines for pharmacoeconomic analysis (Weinstein et al. 1996), our economic model does not include indirect costs related to lost productivity as they are likely to be captured in the utility weights

assigned by patients to depressive state, and would therefore be double counted if included as costs as well. Moreover the amount of these costs is seemingly modest in only 12 weeks.

Attrition. A number of patients are expected to drop out from treatment before follow-up endpoint. Dropout figures are based on the STAR*D sample (Warden et al. 2007) and vary from 7% in remitters to 36% in patients who do not remit. Overall dropout rate is 26%.

Quality of life. Utility, scored on a 0 (death) to 1 (perfect health) continuum, reflects the amount of HRQoL linked to a given health state. Utility is correlated to severity of depressive symptoms – the more severe symptoms, the lower utility score – and it increases from acute to remitted depression. Utility ranges from 0.20 to 0.40 in severe depression and from 0.55 to 0.65 in moderate depression (Revicki and Wood, 1998). Therefore we assign 0.40 to our case-mix of severe and moderate depressive states, ranging from 0.30 to 0.60 in sensitivity analysis. In addition we assign 0.88 (0.80–1.0) to remitted depression (Revicki and Wood 1998). Subjective side effects spontaneously reported by patients include impaired sexual functioning, sleepiness and weight gain for SSRI drugs (Cascade et al. 2009). Elevated rates of dry-mouth, insomnia and hyperhidrosis were mentioned by patients treated with bupropion (Hewett et al. 2010). Instead, sexual dysfunction is rare and bupropion has been proposed to treat SSRI-related sexual dysfunction (Nieuwstraten and Dolovich 2001). Notwithstanding such differences, SSRI drugs and bupropion have comparable levels of tolerability, leading to similar discontinuation rates (Gartlehner et al. 2008). Therefore utility scores is diminished by 0.04 points (0–0.06) to reflect side effect burden with citalopram or bupropion (Revicki and Wood 1998). HRQoL measure is quality-adjusted life week (QALW), which corresponds to 1 week spent in perfect health (utility = 1). To calculate QALWs, utility score associated with each health state is multiplied by the number of weeks spent in the state.

Algorithm A. We estimate a 33% remission rate as reported in the STAR*D sample (Rush et al. 2006). Treatment allocation is based on prescription patterns for antidepressant drugs in Italian samples (Poluzzi et al. 2004; Grassi et al. 2009): two-thirds of patients are treated with citalopram, one-third receive bupropion.

Algorithm B. From our meta-analysis we estimate the distribution of 5-HTTLPR genotypes (l-allele = 77%; s/s genotype = 23%) and the association of this

polymorphism with SSRI response (OR = 2.37) (Serretti et al. 2007,b). Algorithm B, tailoring drug selection to the most favorable 5-HTTLPR profile, should increase antidepressant response and tolerability. To estimate theoretical gain in antidepressant response, we start from a difference of 22% favouring the 5-HTTLPR l-allele over the s/s genotype (Serretti et al. 2007a,b). From this differential response, remission would occur in 38% of our l/l + l/s patients treated with citalopram as opposed to only 16% of the s/s genotype. Conversely, we assume the baseline remission rate for all patients who receive bupropion regardless of 5-HTTLPR genotype. If antidepressant selection was not modified by genetic information (algorithm A), we estimate, 36.3% of patients who possess the l-allele and 21.7% of those with the s/s genotype would remit. Hypothetically, 38% of the l-patients treated with citalopram and 33% of the s/s patients treated with bupropion would remit under algorithm B. This corresponds to a 3.9% increase in remission rate in the whole cohort. A similar procedure is used to estimate gain in tolerability. We postulate that difference in side-effect burden for taking citalopram is still 22% between patients who have at least one l-allele copy, and those without any l-allele. This assumption is conservative looking at studies which suggest that the 5-HTTLPR polymorphism may have a stronger impact on tolerability compared to antidepressant response (Murphy et al. 2004). From this, we estimate a slightly lower treatment related disutility (0.039) in l-allele carriers taking citalopram, which raises to 0.046 in s/s homozygotes at increased risk for adverse effects (Table II). Finally, we calculate a 0.0017 point reduction in side effect burden under algorithm B.

Cost-utility analysis

Using assumptions and estimates as reported above, we compared two treatment strategies that produced different outcomes and, therefore, different QALWs. The aim of cost-utility analysis (CUA) was to ascertain whether the additional cost of performing genetic test could be compensated by benefits it produced in terms of clinical improvement and HRQoL. CUA outcome was the ratio between the difference in costs and the difference in benefits of test and control interventions (incremental cost-effectiveness ratio, ICER):

$$\text{ICER} = (\text{CB} - \text{CA}) / (\text{QB} - \text{QA})$$

C: costs; Q: QALWs;
A: algorithm A; B: algorithm B

Sensitivity analysis

All parameters in a decision-analytic models are variable quantities with known ranges of possible

Table II. Side-effect burden (disutilities) and remission rates with and without genetic test.

Genotype frequencies	Side effect disutilities		Remission rates	
	l/l + l/s (77%)	s/s (23%)	l/l + l/s (77%)	s/s (23%)
Bupropion	0.040	0.040	0.330	0.330
Citalopram	0.038	0.046	0.380	0.160
Algorithm A	0.039	0.044	0.363	0.216
Algorithm B	0.038	0.040	0.380	0.330

Algorithm A: 67% citalopram and 33% bupropion (Grassi et al. 2009).

Algorithm B: l/l+l/s (77%) citalopram and s/s (23%) bupropion (Serretti et al. 2007).

Basal remission rate was 0.33 (Rush et al. 2006). We postulated a 22% difference in response to citalopram between l-allele carriers (Gr1) and s/s genotype carriers (Gr2) based on our previous meta-analysis (Serretti et al. 2007). We estimated remission rates in Gr1 and Gr2 without performing genetic test (algorithm A). Then we estimated remission rates by genotype groups using genetic information to select antidepressant treatment (algorithm B): 0.38 in Gr1 treated with citalopram; 0.33 (basal remission rate) in Gr2 treated with bupropion, whose effects should not be modulated by the 5-HTTLPR polymorphism. A similar procedure was used for side-effect burden. It was 0.04 under basal conditions (Revicki and Wood 1998). Difference between Gr1 and Gr2 was still 22% (see Methods).

Algorithm B-Algorithm A: remission rate=3.9%, side effect burden = -0.0017.

values and associated distribution functions. Base-case value is one such value. Sensitivity analysis is performed to deal with uncertainty in base-case estimates. To do so, it is necessary to assign a probability distribution to each variable. Using a methodology common to previous studies (Shaw and Zachr 2002; Andronis et al. 2009), continuous variables such as drug doses and LOS are assumed to have a normal distribution. The upper limit (UL) and lower limit (LL) of distribution are included in sensitivity analysis. The UL and LL are estimated to be mean \pm 2SD, available from original sources (Rush et al. 2006; OECD 2009). The number of visits and costs are also normally distributed but their SDs are not known. We set the UL and LL to 1.5 and 0.5 times the baseline value (mean) and calculate standard error (SE) from the following equation (1): $SE = (UL-LL)/(2 \times 1.96)$ (Shaw and Zachr 2002). Outcomes (remission; dropouts), hospitalization rate and utilities, which vary over a 0–1 range, are assumed to have a beta distribution (Andronis et al. 2009). Besides minimum and maximum values, the beta distribution has two positive shape parameters, α and β . Its mean and standard deviation are calculated as follows (Jewell 2004):

$$\text{mean} = \alpha/(\alpha+\beta) \quad (2)$$

$$SD = \sqrt{(\alpha\beta)/(\alpha+\beta)^2(\alpha+\beta)} \quad (3)$$

Literature sources provide the UL and LL for remission rate (Cuffel et al. 2003) and utilities and disutility (side-effect burden) score (Revicki and Wood 1998). We set the mean of the distribution equal to the baseline value. SD is equal to the SE as estimated using Equation (1) (Shaw and Zachr 2002). Then we solve Equations (2) and (3) simultaneously for α and β . A modified beta distribution, called beta-PERT distribution, is used to model dropout and hospitalization rates. This distribution is defined by minimum, maximum and most likely (mode) values. Minimum and maximum hospitalization rates are drawn from literature sources (Banks et al. 1998). Mode is calculated as follows: $\text{mode} = \min + (\max-\min)/3$ (Golenko-Ginzburg 1988). Dropout rate is estimated in remitting and non-remitting patients from the STAR*D study (Warden et al. 2007). Minimum dropout value is set equal to 0.5 times the baseline value. The upper value is calculated as reported above (Golenko-Ginzburg 1988). A log-normal distribution is ascribed to odds ratio values (Andronis et al. 2009) that represent the association between 5-HTTLPR and SSRI response. Mean OR for base-case and the UL are derived from our meta-analysis (Serretti et al. 2007a). The LL is set equal to 60% of the baseline OR (see Discussion). Using these criteria to sample uncertainty, we performed one way analysis and, secondarily, a probabilistic sensitivity analysis using Monte Carlo simulations to account for multivariate correlations between parameters (Shaw and Zachr 2002). We run 100,000 trials for simulation using the commercial software Crystal Ball by Oracle (www.oracle.com). In order to better reflect real world situations, we established a negative correlation ($r = -0.8$) between the length of hospital stay and the number of outpatient visits. Similarly it was hypothesized that utility score was negatively correlated (-0.6) with the size of 5-HTTLPR effect. In fact drug-placebo differences in antidepressant efficacy increase as a function of baseline severity (Kirsch et al. 2008). This could imply a stronger impact of biological genetic component on severe depression. Of note, trials that were conducted in tertiary centres, where several patients had severe or psychotic depression, reported higher odds ratios for pharmacogenetic effects than naturalistic studies conducted in primary/secondary settings (Serretti et al. 2007a; Mrazek et al. 2009). We also modeled a negative correlation (-0.6) between the utility of depression and the length of hospital stay (Rocca et al. 2010), whereas treatment-related disutility was positively correlated with dropout rate (0.8). One-way sensitivity analysis was firstly conducted under assumption that the 5-HTTLPR gene controlled clinical response to SSRI drugs and, secondarily,

considering its joint effect on antidepressant response and tolerability. Multivariate sensitivity analysis was carried out on a single major depressive episode and replicated on recurrent episodes. Finally, we plotted a cost-effectiveness acceptability curve (CEAC) to represent incremental cost-effect pairs in the most favourable scenario (two recurrent episodes). A CEAC shows the probability that an intervention is cost-effective compared with the alternative, given the observed data, for a range of maximum monetary values that a decision maker might be willing to pay for a particular unit change in outcome (Fenwick and Biford 2005). More simply, CEAC is a graphical representation of the probability that ICER value falls below an established acceptability threshold.

Results

Sample characteristics are reported in Table I. Baseline parameters and variation ranges for sensitivity analyses are reported in Tables IIIA and IIIB.

Table IIIA. Parameters: baseline values and sensitivity analysis ranges.

	Baseline	SD	Sensitivity analysis
Dose of citalopram (mg/day) ^A	41.8	16.8	8.2–75.4 ^o
Dose of bupropion (mg/day) ^A	282.7	104	74.7–490.7 ^o
Days spent in hospital ^B	21.0	15.0	0.0–51.0 ^o
Cost of citalopram (20 mg) ^C	0.65	0.16*	0.32–0.97
Cost of bupropion (150 mg) ^C	1.25	0.32*	0.62–1.87
Cost of one visit ^D	31.9	8.14*	15.9–47.8
Cost of one day in hospital ^D	238.7	60.9*	119.4–350.7
Cost of genetic test ^E	233.8	59.6*	141.9–325.6
Visits (outpatient remitters)	8.0	2.04*	4–12
Visits (outpatient nonremitters)	12.0	3.06*	6–18
Visits (inpatient remitters)	5.0	1.28*	2.5–7.5
Visits (inpatient nonremitters)	9.0	2.30*	4.5–13.5

All variables were assumed to be normally distributed. Mean was set equal to the baseline value. ^oWe included the lower (–2SD) and upper limits (+2SD) in sensitivity analysis.

*We set the LL and UL to 0.5 and 1.5 times the baseline value, respectively. SD was set equal to the standard error SE: $SE = (UL - LL) / (2 \times 1.96)$ (Shaw and Zachr 2002).

Sources. (A) STAR*D study (Rush et al. 2006); (B) Organization for Economic Co-operation and Development (OECD) Health Data; (C) Electronic version of the Italian *Prontuario Farmaceutico* (www.prontuariofarmaceutico.it); (D) WHO_CHOICE project (www.who.int/choice/en/); (E) Istituto Superiore della Sanità (www.iss.it). Costs are expressed in international dollars (year 2010).

Table IIIB. Probabilities, utilities and 5-HTTLPR effect size (antidepressant response). Baseline values and sensitivity analysis ranges.

	Distribution	Baseline	Sensitivity anal. LL-UL
Remission rate (no genetic test) ^o	Beta	0.33	0.27–0.39
Dropout rate in remitters**	Beta-PERT	0.07	0.035–0.14
Dropout rate in nonremitters**	Beta-PERT	0.36	0.18–0.72
Hospitalization rate*	Beta-PERT	0.12	0.08–0.19
Utility for acute depression ^o	Beta	0.40	0.30–0.60
Utility for remitted depression ^o	Beta	0.88	0.80–1.00
Treatment disutilities ^o	Beta	0.04	0–0.06
5-HTTLPR odds ratio***	Log-normal	2.37	1.40–3.58

^oBeta distribution. Baseline value was set equal to the mean of the distribution. UL and LL were derived from the literature and SD, equal to standard error, was calculated as follows: $SE = (UL - LL) / (2 \times 1.96)$. Then we solved the following equation $mean = \alpha / (\alpha + \beta)$ and $SD = \sqrt{(\alpha\beta) / (\alpha + \beta)}$ simultaneously for α and β Baseline remission rate (Rush et al. 2006); Remission rate variation range (Cuffel et al. 2003) utilities/disutilities (Revicki and Wood 1998).

*Beta-PERT distribution. The LL and UL were drawn from the literature (Banks et al. 1998). The baseline value, equal to mode, was calculated as follows: $mode = min + (max - min) / 3$ (Golenko-Ginzburg 1988).

**Beta-PERT distribution for dropout rates. Baseline values were drawn from the STAR*D study (Warden et al. 2007). The LL was set equal to 0.5 times the baseline value. The UL was calculated by Golenko-Ginzburg's formula (Golenko-Ginzburg 1988).

***Log-normal distribution (OR). The natural logarithm of baseline OR was set equal to the mean of the distribution. The natural logarithms of the LL and UL were set equal to 95%CI values. Baseline OR and the UL were drawn from our meta-analysis (Serretti et al. 2007). The LL was 60% of the baseline OR (see discussion).

Base-case analysis

We firstly tested the model against a genetic influence on antidepressant response only (effect A). From the estimated 3.9% increase in remission, incremental HRQL due to genetic test (algorithm B) was 0.062 QALWs after adjusting by dropout rate. Costs were \$1,005.25 and \$1,230.99 for algorithms A and B, respectively. Incremental cost was \$225.7. ICER was \$3,590. Then we corrected utility scores under algorithm B conditions to account for genetic effect on tolerability (effect B). We subtracted 0.0383 points (instead of 0.04) to reflect side effect burden induced by antidepressant treatment (see above). This was consistent with 4.25% of side effect variance explained by the 5-HTTLPR gene. Algorithm A estimates were not corrected. Incremental HRQL due to genetic test raised to 0.078 QALWs, with

0.016 QALWs due to reduced side-effect burden. The inclusion of side effects in the model determined a lower ICER of \$2,890. Finally, we analyzed the impact of genetic testing strategy on recurrent MDD. We made the following assumptions:

- the same gain produced by algorithm B in the first episode (0.062 QALWs) was expected for every subsequent episode;
- the cost of genetic testing (\$233.8) was charged only once;
- for every episode following the first one, we charged \$997.05 and \$1005.25 to algorithm A and B respectively (the same costs of the first episode, apart from that of genetic test).

This allowed us to estimate that two episodes were needed to obtain an ICER equal to \$1,730. If we considered joint effect on antidepressant response and tolerability, 1.7 episodes were needed to obtain an ICER equal to \$1,657. When such a joint effect was analyzed in two recurrent episodes, we obtained an ICER value of \$1,392. In the first one way analysis it was assumed that only antidepressant response was under genetic control. Severity of depression, the strength of 5-HTTLPR effect and cost for genetic test emerged as important determinants (see Table IV). We then analyzed the joint effect of 5-HTTLPR variants on antidepressant response and tolerability. Sensitivity analysis was carried out assuming a 1–15% range of side effect variance explained by the 5-HTTLPR gene (Kato and Serretti 2010). ICER estimate ranged from \$4,400 to \$2,190. Model parameters were then varied simultaneously to analyze their interrelations. 100,000 bootstrap (Monte Carlo) trials were run to obtain a probability distribution of ICER values (Figure 1). Estimated ICER ranged from \$57 to \$18,992. Mean and median ICER were \$2,834 (± 944) and \$2,693 respectively. This analysis was replicated considering two recurrent

episodes (Figure 2). Estimated ICER ranged from \$90 to \$7,625. Mean and median ICER were \$1,372 (± 482) and \$1,304 respectively. CEAC (two recurrent episodes) is displayed in Figure 3.

Discussion

Pharmacogenetic studies report a large number of candidate genes that can modulate antidepressant response. Most genes are not supported by consistent evidence (Drago et al. 2009). For those that have emerged as sufficiently strong factors (e.g., the 5-HTTLPR polymorphism) it remains unclear whether their impact on antidepressant response is as meaningful as to use genetic testing in clinical practice to identify likely responders a priori. To the purpose, we developed a multivariate theoretical decision analytic model to select antidepressant treatment under guidance from 5-HTTLPR genetic test. An algorithm matching serotonin reuptake inhibitors or noradrenergic/dopaminergic agents to patients' 5-HTTLPR status was compared with a routine procedure for antidepressant selection in a cost-utility analysis. The model was based on Italian mental health setting and incorporated a large number of real world parameters. Treatment cohort included patients of Caucasian origin with moderate to severe MDD. Indeed the association between 5-HTTLPR variants and SSRI response was found to be consistent in Caucasian samples but not in other ethnic groups (Serretti et al. 2007a,b). We summarize the main characteristics of our simulation and discuss their implications for future economic studies.

(1) To our knowledge, there are no experimental data about effective gain in antidepressant response due to pharmacogenetic approach. Our estimate, based on meta-analytic data (Serretti et al. 2007a), was 3.9%. A slightly higher value, 4.6%, was reported by Smits and coll. using a similar decision-analytic model (Smits et al. 2007) and smaller estimates, concerning however the effect of a genetic marker on antidepressant response but not the benefit of genetic test, were reported in naturalistic samples (Mrazek et al. 2009). Sensitivity analyses included a very conservative effect size. We assumed that patients with the s/s genotype treated with citalopram would have the greatest benefit from genetic testing, quantifiable as 22% increase in remission rate (Table II). This value is the approximate difference observed between placebo and antidepressant therapy (Walsh et al. 2002). This would imply virtually all the antidepressant response in the 5-HTTLPR s/s genotype group was due to a placebo response and none to the SSRI antidepressant in these patients. That seems

Table IV. One-way sensitivity analysis. 5-HTTLPR effect on antidepressant response.

	Range	ICER range
Prob. Hospitalization	0.9–10%	4,742–4,742
Utility score (acute MDD)	0.35–0.75	2,420–13,173
Utility score (remitted MDD)	0.80–1.00	5,646–2,892
Side effect burden (disutility)	0–0.06	4,742–4,742
Remission rate (no genetic test)	0.27–0.39	4,742–4,742
Dropout in remitters	0.035–0.14	4,742–4,742
Dropout in non-remitters	0.18–0.72	4,602–5,051
5-HTTLPR odds ratio	1.53–3.58	9,917–3,436
Cost of genetic test	142–326	2,808–6,685

One-way sensitivity analysis showed that depression severity, size of 5-HTTLPR effect and cost of genetic test caused the greatest ICER variations.

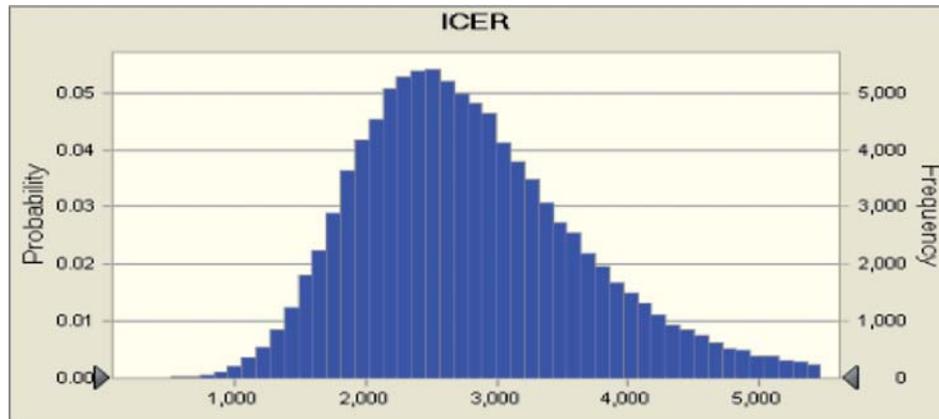


Figure 1. Probability distribution of ICER values (single episode). Genetic control of antidepressant response + tolerability. Single major depressive episode. All model parameters were varied simultaneously. Each parameter was randomly assigned a value within its variation range. The cycle ended with ICER calculation. This curve represents the probability distribution of ICER values after 100,000 cycles. ICER was estimated to range from \$1,800 (10th percentile) to \$4,041 (90th percentile). Mean and median ICER were \$2,834 (± 944) and \$2,693, respectively. Baseline ICER was \$2,515.

unlikely since differences in response between placebo and 5-HTTLPR s/s genotypes have been reported (Reimherr et al. 2010). Further, placebo response was found to be higher in l-allele carriers compared to the s/s genotype, like antidepressant response (Rausch et al. 2002). Therefore, at best estimate, 50–60% of change in response outcome might be due to a true pharmacologic effect. This would reduce improvement under pharmacogenetic approach to 1.9%, while the association between 5-HTTLPR and antidepressant response would have an odds ratio of 1.4. This value is more consistent with similar monogenetic traits of psychiatric disorders (Kendler 2005). Moreover most of the current pharmacogenetic findings have odd ratios for individual alleles or genotypes of 1.5–2 on average

(Arranz and Kapur 2008). In terms of HRQL, our algorithm incorporating genetic test produced an additional 0.062 QALW (effect A). The difference between remission and lack of remission was 1.9 QALWs. This suggests that 3.2% of variance in antidepressant response might be due to the 5-HTTLPR polymorphism. This is consistent with the effect of single genetic markers on complex psychological phenotypes (Comings et al. 2000). Side-effect burden could be reduced by 0.0017 points if antidepressant selection was based on 5-HTTLPR test (effect B). This result was obtained assuming a similar impact of 5-HTTLPR on SSRI response and tolerability (Murphy et al. 2004). This finding would relate 4.2% of side-effect burden to 5-HTTLPR polymorphism.

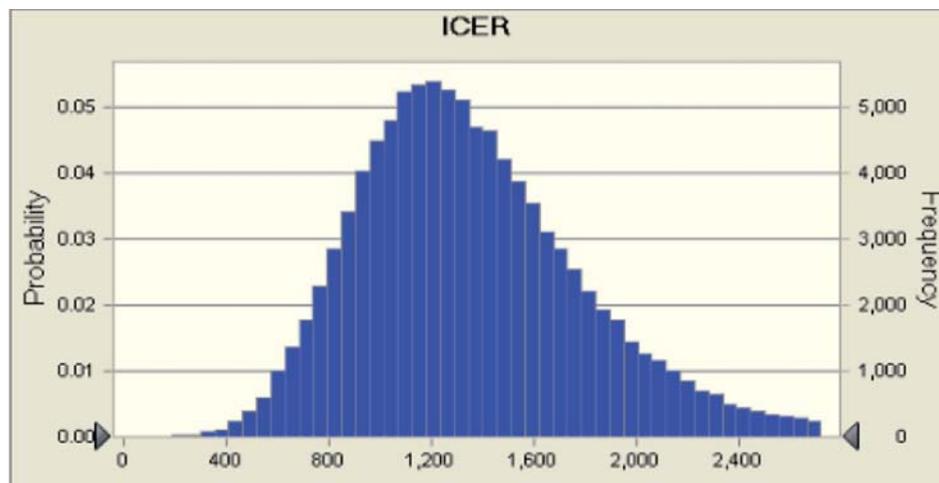


Figure 2. Probability distribution of ICER values (two recurrent episodes). Genetic control of antidepressant response + tolerability. Two recurrent major depressive episodes. This curve represents the probability distribution of ICER values after 100,000 cycles. ICER was estimated to range from \$837 (10th percentile) to \$1,982 (90th percentile). Mean and median ICER were \$1,372 (± 482) and \$1,304, respectively. Baseline ICER was \$1,212.

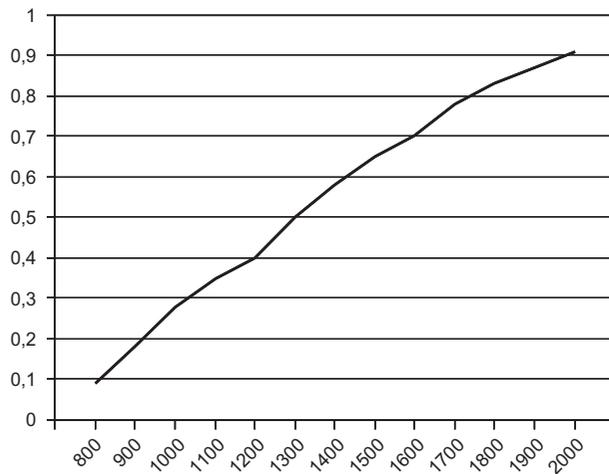


Figure 3. CEAC (two recurrent episodes). CEAC shows the probability (axis Y) that ICER value falls below an established threshold (axis X). In the United States a common cost-effectiveness threshold is \$50,000 per QALY gained (\$961 per QALW). The probability of having an ICER value below this threshold is slightly higher than 20%. The World Health Organization suggests a threshold as high as three times GDP (Italy: \$1,769 per week). The probability of having an ICER value below this threshold is higher than 80% (see discussion).

(2) Previous studies identified genetic test cost and test effect size as critical factors (Perlis et al. 2009). We acknowledge the importance of these variables, that caused the greatest ICER variations in this simulated analysis along with depression severity, but also emphasize a multitask perspective for genetic test use. Since the 5-HTTLPR s-allele is associated with a poorer response to SSRI drugs as well as a greater side-effect burden, the same genetic profile could be used to choose an antidepressant that is both effective and well-tolerated. To represent this feature we pooled effects A and B in our decision-analytic model. This allowed to improve its cost-utility (ICER decreased from \$3,590 to \$2,890). We argue the same gene may have a small impact on different phenotypes relevant to clinical practice. Thus, from a single test, we could collect information on different targets and levels of treatment (e.g., pharmacotherapy; psychotherapy). Genetic information could then be reused to prevent relapse after exposure to risk factors or modify treatment if concurrent medical conditions are present. This study focused on antidepressant response and side effects. However the 5-HTTLPR polymorphism has also been found to moderate depressive response to environmental stress (Caspi et al. 2003; Lazary et al. 2008). Individuals with the short allele exhibited more depressive symptoms, diagnosable depression and suicidality in relation to stressful life events (Caspi et al. 2003). This effect, although (most likely) smaller than initially reported (Munafò et al. 2009),

could be used to plan psychotherapy in individuals exposed to stressful events in order to prevent depressive relapse. Other multitask genes code for tryptophan hydroxylase and 5-HT_{2A} receptor. The TPH gene has been also associated with antidepressant response (Serretti et al. 2004) and suicidality (Turecki et al. 2001; Bellivier et al. 2004). The 5-HT_{2A} gene is involved in antidepressant response (McMahon et al. 2006; Kato et al. 2009) and tolerability (Kato and Serretti 2010).

(3) MDD is characterized by a high rate of recurrence. In the large STAR*D sample, 76% of patients had recurrent MDD and a mean of 6 episodes in 15 years (Rush et al. 2006). Pharmacoeconomic studies have usually analyzed the impact of a target intervention on a single episode and then benefits for a longer period, often 6 months or 1 year. In the previously mentioned study Perlis et al. (Perlis et al. 2009) studied a time horizon of 3 years. A small outcome improvement would justify a costly intervention if it lasting for such a long period. So, a long follow-up was methodologically correct but it constitutes a serious hurdle to build a realistic model. Firstly, because only a minority of patients do not drop out from treatment after a few months (Demyttenaere et al. 2001; Melartin et al. 2005; Sawada et al. 2009). Secondly, even in those who remain in treatment, adherence is seldom at optimal level, and this may have negative consequences for effectiveness and cost (Stein et al. 2006; Tournier et al. 2009; Serna et al. 2010). For a long-term assessment of major depressive disorder it is necessary to estimate recurrence rate. This is not an easy task, because follow-up studies of depression are characterized by marked differences in terms of designs, outcome definitions and crude measures of pharmacotherapy (Hughes and Cohen 2009). A further challenge is resistant depression. Most sequential algorithms suggest dual antidepressants that act on the serotonin and norepinephrine systems or add on treatment with norepinephrine uptake inhibitors as second line approaches after failure of SSRI monotherapy in major depression (Gaynes et al. 2008). If we assume, as reported above, that the effect of 5-HTTLPR is consistently demonstrated for SSRIs but not for other antidepressant drugs, initial benefit of pharmacogenetic approach might be nullified by subsequent drug switch. For all these reasons, we restricted our evaluation to an interval of 12 weeks. This period corresponds to the length of many pharmacological trials of acute phase treatment of major depression (Serretti et al. 2005). Moreover it was recommended as an adequate follow-up period for pharmacogenetic studies (Serretti et al. 2007b). Nevertheless, rather than tracing the course of depression in a defined interval of months or years, we pooled benefits and

costs in recurrent episodes. We demonstrated that pharmacogenetic approach was associated with a significant gain in cost-effectiveness after two episodes. To date, clinical decisions in recurrent MDD are influenced by treatment history (Zetin et al. 2006; Bauer et al. 2008). Unfortunately, most patients have difficulty remembering past trials, in particular when two or more medications were taken concurrently (Posternak and Zimmerman 2003). Genetic data could therefore make up for this lack of information. Genetic test is performed once and its results used to choose the most appropriate treatment in subsequent episodes. In spite of the oversimplification observed in most clinical trials, in real world antidepressant response is affected by a large number of co-acting variables. To account for this complexity, we analyzed interactions between model parameters in a multivariate framework. This represents an advantage of our study over previous ones that analyzed each parameter separately (Perlis et al. 2009). On the other hand we are aware of some caveats mainly affecting the reliability of decision-analytic model. The influence of 5-HTTLPR on SSRI response is documented in randomized trials, but biased by various limitations (Serretti et al. 2007b), whereas less clear evidence comes from naturalistic studies (Mrazek et al. 2009), and its real effect is not completely established yet (Taylor et al. 2010). We posited that sensitivity to 5-HTTLPR variants was equivalent for all SSRIs and we drew it from meta-analytic data. However recent studies emphasize subtle differences between individual SSRI drugs (Kato et al. 2005). Moreover serotonergic activity has a positive impact on specific depression symptoms (Eker et al. 2009). 5-HTTLPR may not affect response to noradrenergic antidepressants. This hypothesis, central to the architecture of our model, is supported by an increasing number of studies (Pollock et al. 2000; Huezo-Diaz et al. 2009; Min et al. 2009), but it cannot be considered an established finding. This could have overestimated the benefit of pharmacogenetic approach. Conversely, the choice of a 12-week horizon for cost-utility analysis is very conservative, since patients who succeed in remitting from a major depressive episode have a satisfactory well-being and a good level of functioning for several months. Median time to relapse in full remitters was in fact reported to be 231 weeks (Judd et al. 1998). In the STAR*D sample, three quarters of patients who remitted with the first antidepressant treatment did not relapse in the following 12 months (Rush et al. 2006). These long-term benefits of our treatment approaches were overlooked by a few weeks follow-up, although assessing recurrent episodes could in part compensate this loss. Our model did not account for recent discoveries that changed

the structure and function of the 5-HTTLPR polymorphism. Patients who harbor the L_G allele (rs25531) might be less likely to respond to SSRIs (Mrazek et al. 2009) and have more side effects (Hu et al. 2007) like S-allele (5-HTTLPR) carriers. This would increase the number of patients who benefit from pharmacogenetic approach. More recently it was reported that the BDNF MET allele, which was predicted to have reduced responsiveness to 5-HT signalling, could be protective against 5-HTTLPR S allele-induced effects on a brain circuitry encompassing the amygdala and the subgenual portion of the anterior cingulate (Pezawas et al. 2008). These findings might improve the role of 5-HTTLPR, but, so far, their implications remain unclear. To simplify the association between 5-HTTLPR variants and antidepressant response, second-order interactions with gender (Smits et al. 2008) and life-events (Keers et al. 2011) were not featured. Other missing information includes costs to caregiver or other family members and psychotherapy. We used typical starting doses for SSRI treatment. These might be suboptimal and interfere with the assessment of clinical response (Papakostas et al. 2010). The impact of antidepressant treatment on suicidal risk (Kasper et al. 2007) and physical morbidity (e.g., cardiovascular diseases) (Koponen et al. 2010) was not featured. Our model was implemented to ascertain whether incorporating genetic information in antidepressant treatment could increase HRQoL as much as to compensate incremental cost. These results are only provisional because key assumptions regarding gain in antidepressant response and reduction in side-effect burden are speculative, though reasonable, and not supported by empirical findings. Assuming an incremental \$50,000 per quality-adjusted life year (\$961 per QALW), that is often used as a threshold ICER in the United States (Azimi and Welch 1998), genetic test was not cost-effective under base-case assumptions. In sensitivity analysis, the probability that ICER value fell below \$961 per QALW threshold was slightly higher than 20% in the most favourable scenario (two recurrent episodes) (see Figure 3, CEAC). For interventions that cost \$60,000 to approximately \$175,000 per QALY, certain decision makers may find the interventions sufficiently efficient; most others will not agree (Azimi and Welch 1998). Our simulation placed ICER related to genetic test strategy in this range of discordant interpretation. Following the recommendations of the Commission on Macroeconomics and Health, the World Health Organization (<http://www.who.int/choice/en/>) uses gross domestic product (GDP) as a readily available indicator to derive the following three categories of cost-effectiveness: Highly cost-effective (less than GDP per capita);

Moderately cost-effective (between one and three times GDP per capita); and Not cost-effective (more than three times GDP per capita). This results in two lower and upper (ceiling) cost-utility thresholds (CUT) that are different by WHO regions. Italy's CUTs (European region A) are therefore \$750 and \$1,769 respectively on a weekly basis. Neither single parameters analyzed one-by-one, nor the network of all parameters could shift ICER below such thresholds in one MDD episode. However estimated ICER was inferior to upper CUT in two recurrent episodes. CEAC shows that the probability of having an ICER value below 3GDP threshold was >80%. This might suggest a moderate cost-effectiveness of performing genetic test under best conditions.

In conclusion, notwithstanding a number of caveats, this study presented the most complex and close to real world theoretical model available to date to use genetic data in order to select antidepressant treatment. The model combines effects on drug response and tolerability, evaluated in recurrent episodes of depression. This model is an example of multitask use of genetic testing. The patient is tested once and collected information is applied to different clinical targets, simultaneously or sequentially. This is a promising approach to transfer pharmacogenetics from research to clinical practice although it is premature to conclude that genetic tests should be included in antidepressant treatment. We argue our model will be useful for further economic studies.

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None.

Statement of Interest

None to declare.

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