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Should pharmacogenetics be incorporated in major depression treatment? Economic evaluation in high- and middle-income European countries

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ABSTRACT

The serotonin transporter 5-HTTLPR polymorphism moderates response to SSRIs and side-effect burden. The aim of this study is to quantify the cost-utility of incorporating 5-HTTLPR genotyping in drug treatment of major depressive disorder (MDD). We previously reported a theoretical model to simulate antidepressant treatment with citalopram or bupropion for 12 weeks. The drugs were alternatively selected according to an 'as usual' algorithm or based on response and tolerability predicted by 5-HTTLPR profile. Here we apply this model to conduct a cost-utility analysis in three European regions with high GDP (Euro A), middle GDP (Euro B) and middle-high GDP (Euro C).. In addition we test a verification scenario in which citalopram + bupropion augmentation is administered to individuals with the least favorable 5-HTTLPR genotype. Treatment outcomes are remission and Quality Adjusted-Life Weeks (QALW). Cost data (international $, year 2009) are retrieved from the World Health Organization (WHO) and national official sources. In base-case scenario incremental cost-effectiveness ratio (ICER) values are $1147 (Euro A), $ 1185 (Euro B) and $1178 (Euro C). From cost-effectiveness acceptability curve (CEAC), the probability of having an ICER value below WHO recommended cost-utility threshold (3 GDP per capita = $1926) is >90% in high-income countries (Euro A). In middle- income regions, these probabilities are <30% (Euro B) and <55% (Euro C) respectively. All estimates are robust against variations in treatment parameters, but if genetic test cost decreases to $100, pharmacogenetic approach becomes cost-effective in middle-income countries (Euro B). This simulation using data from 27 European states suggests that choosing antidepressant treatment from the results of 5-HTTLPR might be a cost-effective solution in high income countries. Its feasibility in middle income countries needs further research.

1. Introduction

Major depressive disorder (MDD) affects approximately 1 in 5 adults worldwide (Ustun et al., 2004). MDD is a serious threat to population, not only in terms of increased mortality from suicide (Bradvik et al., 2008; Moller, 2003), but also because it is a main determinant of health expenditure (Watkins et al., 2009) and a leading cause of work disability (Adler et al., 2006; Bender and Farvolden, 2008; Rytsala et al., 2005). Moreover health-related quality of life (HRQoL) in MDD is inferior to the general population (Aydemir et al., 2009; Sapin et al., 2004), and comparable with the burden in severe physical disorders (Buist-Bouwman et al., 2006; Soeteman et al., 2005). Although antidepressant drugs have proven to be effective in terms of symptom improvement as well as HRQoL gain (Llorca and Fernandez, 2007; Sarnes and Frankum, 2004; Sullivan et al., 2004), approximately one third of patients with MDD still fail to respond to a correctly delivered antidepressant treatment and only 20%–40% achieve remission in real world conditions (Ferrier, 1999). It is now acknowledged that antidepressant response is affected by genetic factors (Kato and Serretti, 2010; Kim et al., 2006; Laje et al., 2009; Serretti et al., 2007; Villafuerte et al., 2009). Pharmacogenetics 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 favorable genetic profile, the number of responders would be increased. So far this is a mere hypothesis not supported by real trials. However it is possible to estimate theoretical gain in antidepressant response if genetic information is used for drug selection based on literature data and, along with this, to perform a cost-effectiveness analysis (Perlis et al., 2009). This is the design of our study. Ideally, this analysis should include areas at different economic level. In

Abbreviations: MDD, major depressive disorder; HRQoL, health-related quality of life; GDP, gross domestic product; PPP, purchase power parity; CUA, cost-utility analysis; QALW, quality-adjusted life week; ICER, incremental cost-effectiveness ratio; CEAC, cost-effectiveness acceptability curve; WHO, World Health Organization; CHOICE, Choosing Interventions that are Cost-effective; SSRI, specific serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

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fact interventions that are cost-effective in a country setting, may not be recommendable in another geographical area with a different economic situation. On the other hand, pharmacogenetic analysis requires homogeneity in ethnic stratification. The 27 member-states of the European Union (EU), are relatively homogeneous in their ethnic composition but with substantial differences in economical parameters (gross domestic product, GDP; cost of living) and infrastructure, therefore, in our simulation, cost-effectiveness data were referred to EU countries. In Europe, epidemiological surveys report lifetime figures of MDD ranging from <10% in Mediterranean countries to over 20% in Central and Northern regions (de Girolamo et al., 2006). In 2004 the cost of depression corresponded to 1% of the total economy of Europe (Sobocki et al., 2006). The main cost driver was indirect, due to sick leave and early retirement. (Sobocki et al., 2006). As for the genetic part, we selected the Serotonin Transporter Gene Promoter Polymorphism (5-HTTLPR). A single SNP with only three genotypes could be easily incorporated in an algorithm for antidepressant selection. Moreover one SNP is less expensive than multiple gene tests. The 5-HTTLPR is the best established genetic factor that moderates response to SSRI treatment in Caucasian populations. A large meta-analysis indicated that 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., 2007). The same trend was confirmed for dominant model, that is individuals with the l/l genotype had a better response over the other genotypes, although the effect was weaker (Serretti et al., 2007). 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). Unfavorable variant is still the short allele (Popp et al., 2006). We previously published a theoretical model to compare two algorithms for pharmacological treatment of major depressive disorder based on current practice or incorporating the results of 5-HTTLPR test to choose the most appropriate antidepressant (Serretti et al., 2011). In this second study we apply that model, with some modifications reported below, alongside a cost-utility assessment to ascertain the feasibility of pharmacogenetic approach to antidepressant selection in European regions at different economical development levels.

2. Methods

2.1. Sample and design

This cost-utility analysis is based on a decision model described elsewhere (Serretti et al., 2011). Briefly, a hypothetical cohort of Caucasian adults (18–65 years) with moderate to severe MDD (HAMD17>18) is treated with a serotonin-reuptake inhibitor (SSRI) or a non-SSRI second generation antidepressant (Gartlehner et al., 2008a) for 12 weeks. Available drugs are citalopram 41.8 ± 16.8 mg/d and bupropion: 282.7 ± 104.4 mg/d based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al., 2006a,b). Bupropion is not commonly prescribed in European centers (Bauer et al., 2008). Nevertheless we chose this drug as alternative to SSRI because it acts on the dopamine and norepinehrine systems but not on the serotonin system, thus it is expected to be insensitive to 5-HTTLPR modulation (Serretti et al., 2011). Moreover bupropion and SSRIs have comparable efficacy and general tolerability (Gartlehner et al., 2008b; Papakostas et al., 2008). Control strategy for treatment allocation (algorithm A) is modeled on current practice in most European nations (Bauer et al., 2008), SSRI is first choice. Bupropion is chosen as starting treatment if there is nonreponse to previous SSRI treatment or concern for SSRI-related side-effects (e.g. sexual dysfunction). A likely estimate, consistent with antidepressant prescription patterns (Bauer et al., 2008; Grassi et al., 2009), is two thirds of patients treated with citalopram. Instead bupropion is administered to a larger proportion of patients than in epidemiological samples (Bauer et al., 2008). Test scenario (algorithm B) incorporates the results of 5-HTTLPR genotyping, under hypothesis of a dominant effect of the l-allele. So, patients who possess at least one l-allele, likely responders to SSRI treatment and less burdened by SSRI-related side effects, receive citalopram. Instead individuals homozygous for the short allele, theoretically less responsive to SSRI drugs and with more serious SSRI-related side-effects, are treated with bupropion. Alternatively, all individuals are treated with citalopram at doses reported above, and s/s genotype carriers are also administered bupropion (150 mg/d) augmentation. This strategy (algorithm C) is tested on the most favorable country setting. The effect size of 5-HTTLPR modulation of SSRI response is estimated from a meta-analysis of randomized trials (Serretti et al., 2007). The impact of 5-HTTLPR variants on side-effects (SSRI) is also based on pharmacogenetic studies (Kato and Serretti, 2010). From these data, using a procedure that was detailed in previous work (Serretti et al., 2011), we estimated that remission rate would increase by 3.9 under test strategy (algorithms B and C) whereas side-effect burden would decrease by 0.0017 points. Transition from acute to remitted depression was analyzed by a Markow model, which represents one cycle of eight weeks necessary to achieve remission (cycle A), and four weeks in remitted or nonremitted state (cycle B). Utility score reflecting HRQoL level in transition states was differentiated in the two cycles (Revicki and Wood, 1998). During cycle A all patients in acute depression were assigned a utility of 0.40. In cycle B utility score rose to 0.88 in remitters, whereas it was still 0.40 in patients who did not remit. Side effect burden was expressed as a negative score (0.04 points) that is subtracted from overall utility. A part of the cohort discontinued treatment during cycle B (dropout). These subjects were more often nonresponders (36% vs 7% of remitters)(Warden et al., 2007). Genetic analysis was conducted as reported by Smits et al. (2007). In this new study, setting, care management and costs are different than in previous publication (Serretti et al., 2011).

2.2. Setting

We imagine that the trial and economic evaluation are alternatively conducted in one of the three WHO regions (www.WHO.int/choice) that belong to European Union: Euro A including high-income Western countries such as Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Malta, Netherlands, Portugal, Slovenia, Spain, Sweden, United Kingdom; Euro B that encompasses middle-income South-Eastern countries such as Bulgaria, Poland, Romania and Slovakia; Euro C that encompasses North-Eastern countries with high-middle income such as Estonia, Hungary, Latvia and Lithuania. The characteristics of mental health care are quite different in Western and Eastern European countries. Western countries (region Euro A) have balanced mental health systems. Most patients with major depressive disorder are treated in outpatient facilities, primary care centers or community mental health centers (CMHC). Inpatients facilities are used to treat depression for limited periods of time based on symptom severity or specific health risks (e.g. suicide). In the last three decades, beds in psychiatric hospitals have dramatically fallen in all Western countries. In Italy, Sweden and Iceland there are no longer mental hospitals and inpatient care is provided in psychiatric wards in general hospitals. In Eastern Europe the provision of community care is limited. In some countries (e.g. Slovakia; Romania) community care facilities are not available. Inpatients are admitted to psychiatric hospitals, and, less often, to psychiatric wards in general hospitals. Outpatient care is more commonly provided in hospital centers. General practitioners seldom treat mental disorders (WHO, 2005).

2.3. Care management and costs

Care management is different in Western European and Eastern European countries. In Western countries (Euro A) patients are treated in primary care centers or community mental health facilities (CHMC). Each visit is conducted by a physician and lasts approximately 20 min.

The frequency of visits, established according to published guidelines (American Psychiatric Association, 2000) and similar to psychiatric practice in many European countries, ranges from once weekly in acute depression to once every two months in remitted patients. In Western countries hospitalization rate is estimated to be 12% (Banks et al., 1998), involving the most severe patients and those with suicidal risk. These subjects are admitted to general hospital psychiatric wards in secondary and tertiary-level hospitals (see below). The patients remain in hospital for a few weeks, until stabilization, then they are discharged and followed as outpatients in aforementioned centers. The length of hospital stay (LOS) averages 21 ± 15 days (OECD, 2009). In Eastern Europe transition to a community-care paradigm for mental health is still ongoing (Gater et al., 2005). In our simulation the majority of cases with severe MDD are treated in inpatient facilities. LOS is projected to be 51 ± 10 days (Auffarth et al., 2008). No visits are scheduled after discharge. Based on regional data about mental health systems (OECD, 2009; WHO, 2005), this institutionalized scenario should involve 80% (70%–100%) and 60% (50%–80%) of cases in Euro B and Euro C countries respectively. The rest is treated in outpatient centers as reported above. We estimated direct costs for remitting, non-remitting and dropout patients. Cost drivers were drug acquisition and delivery, outpatient and inpatient care and genetic test. Information on drug prices was collected from the Common European Drug Database (http://cedd.oep.hu/). The baseline prices were drawn from a reference country (Euro A: Austria; Euro B: Slovakia; Euro C: Hungary). The lower and upper limits of price distribution were included in sensitivity analysis. Cost for outpatient and inpatient care was based on World Health Organization data (WHO-CHOICE project. www.who.int/choice/en/). Outpatients were visited in primary care centers or community mental health facilities (CMHC) at comparable levels of cost. As for inpatient stay, different unit-costs were estimated for secondary- and tertiary-level hospitals according to WHO definitions (www.who.int/choice/en/). Instead psychiatric hospitals were comparable to secondary-level hospitals. Further, we estimated a mean cost of $200 for genetic test (Stallings et al., 2006). Cost data were referred to 2009 and converted into international dollars using purchasing power parity (ppp) exchange rates. Cost units for visits and days spent in hospital, available for year 2005, are inflated by 2% yearly (region Euro A) and 6% yearly (regions Euro B and Euro C) respectively, based on mean annual inflation rates reported in EU countries during the period 2005–2009 (CIA-The World Factbook. www.cia.gov).Indirect costs related to productivity loss were not included in CUA, as recommended in guidelines for pharmacoeconomic analysis (Weinstein et al., 1996). In fact 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.

2.4. Cost–utility analysis and sensitivity analysis

Based on simulation reported above, we estimated the probabilities of remission, lack of remission and dropout under algorithms A and B, and attached costs and utilities in state-transition model. This allowed to calculate differential costs and differential utilities in terms of quality-adjusted life weeks (QALW) between the two algorithms, then the ratio between the differential costs and utilities (*incremental cost-effectiveness ratio*, ICER). This was repeated for the three European regions and for two recurrent episodes. So, both costs and utilities, collected for a single episode, were doubled except for genetic test cost that was charged once. This method does not require a long follow up, that could be difficult to simulate under real-world conditions (Serretti et al., 2011). A further difficulty is to obtain a reliable treatment history, that is recommended for the optimal choice of medication (Zetin et al., 2006). In fact most patients are unable to recall all antidepressant trials (Posternak and Zimmerman, 2003). We reasonably assumed that genetic information, collected once, could be used to guide antidepressant selection in subsequent episodes more reliably than treatment history (Serretti et al., 2011). Sensitivity analysis was carried out to deal with uncertainty in base-case estimates of model parameters. Each parameter was assigned a probability distribution: normal distribution for continuous variables such as drug dosages, days spent in hospital, number of outpatient visits and costs; beta distribution for outcomes, hospitalization rate and utilities, which vary over a 0–1 range; log-normal distribution for the effect size of 5-HTTLPR modulation of SSRI response (Serretti et al., 2011). For most parameters variation ranges were derived from the literature: drug dosages (Rush et al., 2006a,b); remission rate without genetic test (Cipriani et al., 2007; Cuffel et al., 2003); dropout rate (Warden et al., 2007); utilities/disutilities (Revicki and Wood, 1998); hospitalization rate (Banks et al., 1998; OECD, 2009); length of hospitalization (Auffarth et al., 2008; OECD, 2009); 5-HTTLPR modulation of SSRI response (Serretti et al., 2007); 5-HTTLPR effect on SSRI tolerability (Hu et al., 2007; Kato and Serretti, 2010). To determine cost variation ranges, the lower limit and upper limit were established to be 0.5 time and 1.5 time the baseline value (Shaw and Zachr, 2002).

A probabilistic sensitivity analysis (Monte Carlo simulation) accounted for interactions between the whole parameters and generated a probability distribution of ICERs for the three European regions. 100,000 trials were run for simulation using the commercial software Crystal Ball by Oracle (www.oracle.com). Cost-effectiveness acceptability curves (CEAC) were plotted to represent incremental cost-effect pairs in each European region. 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). One way sensitivity analysis was performed on the least cost-effective country setting to identify which parameters could significantly increase cost-utility related to pharmacogenetic approach. Finally we compared verification algorithm (scenario C) to algorithm A in the best country setting using the same procedure detailed above. Sensitivity analysis was not performed.

3. Results

The hypothetical cohort, modeled on the STAR*D sample, is reported in Table 1. Costs are reported in Table 2. Probabilities, utilities and 5-HTTLPR effect sizes are reported in Table 3.

3.1. Base-case scenario. Algorithm A vs algorithm B

We transform 3.9% increase in antidepressant response and 0.0017 points reduction in side effect burden (see above) into QALWs adjusting by dropout rate (26% as estimated from the STAR*D) (Warden et al., 2007). Incremental benefit due to pharmacogenetic approach is 0.062 QALWs (antidepressant response) + 0.016 QALWs (side-effect burden). This projects overall incremental benefit to 0.156 QALWs by two recurrent episodes. This value is used to calculate ICER.

Table 1
Characteristics of the cohort.

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

STAR*D sample (Rush et al., 2006a).

Table 2
Direct and indirect costs. Variation ranges are reported in brackets.

	Euro A	Euro B	Euro C
Cost of citalopram (20 mg)	0.37 (0.19–0.56)	0.14 (0.07–0.21)	0.22 (0.11–0.33)
Cost of bupropion (150 mg)	1.09 (0.55–1.63)	0.69 (0.35–1.04)	0.79 (0.40–1.19)
Cost of one visit	34.9 (17.5–52.3)	16.5 (8.25–24.8)	17.8 (8.90–26.7)
Cost of one day in hospital	253 (127–380)	107 (53.5–161)	127 (63.5–191)
Cost of genetic test	200 (100–300)	200 (100–300)	200 (100–300)
ICER thresholds			
Very cost-effective* (<GDP per capita)	642	298	368
Moderately cost-effective* (<3GDP per capita)	1926	894	1104

All costs are expressed in international dollars ($) adjusted by purchasing-power-parity (ppp). Reference year is 2009.
Drug prices are drawn from the Common European Drug Database (CEDD). Reference countries: Austria (Euro A); Slovakia (Euro B); Hungary (Euro C).
Costs for visits and hospitalization are drawn from the WHO_CHOICE Unit costs for patient services table (www.who.int/choice/costs/unit_regions/en/index.html). These costs, available for year 2005, are inflated by mean annual inflation rate observed in each EU region during the period 2005–2009: Euro A: 2% (total increase: 8%); Euro B: 6% (total increase 24%); Euro C: 6% (total increase 24%) (CIA-The World Factbook: www.cia.gov). The cost of genetic test was estimated from published studies (Wedlund and de Leon, 2001). Productivity loss was set equal to weekly GDP per capita (year 2009) (CIA-The World Factbook: www.cia.gov) multiplied by the number of weeks spent in acute depression. Costs were normally distributed. Mean was set equal to the baseline value. The lower limit (LL) and upper limit (UL) of distribution were set to 0.5 times and 1.5 times the baseline value, respectively. Standard error (SE), equal to standard deviation (SD), was calculated as follows: $SE = (UL - LL)/(1.96 \times 2)$ (see Serretti et al., 2011).
*Cost-effectiveness thresholds are based on WHO_CHOICE methodology (see discussion).

Region Euro A. Estimated overall cost is $2063 under algorithm A and $2242 under algorithm B conditions. Algorithm B incremental cost is $179; ICER is $1147.

Region Euro B. 80% of cases are treated in inpatient facilities. Estimated overall cost varies from $8833 under algorithm A to $9018 under algorithm B. ICER is $1185.

Region Euro C. 60% of cases are treated in inpatient setting. Estimated overall cost varies from $7912 under algorithm A to $8096 under algorithm B. ICER is $1179.

3.2. Sensitivity analysis

Multivariate sensitivity analysis in the three European regions

Region Euro A. Estimated ICER values (10th–90th percentile) range from $638 to $1738. Mean and median ICER values are $1155 and $1095 respectively (Fig. 1). CEAC (Fig. 4) shows that the probability of having an ICER value below $1926 cost-effectiveness threshold (see discussion) is >90%.

Region Euro B. Estimated ICER values range from $644 to $1736. Mean and median ICER values are $1156 and $1097 respectively (Fig. 2). CEAC shows that the probability of having an ICER value below $894 cost-effectiveness threshold is <30% (figure not shown).

Region Euro C. Estimated ICER values range from $646 to $1736. Mean and median ICER values are $1157 and $1099 respectively (Fig. 3). CEAC shows that the probability of having an ICER value below $1104 cost-effectiveness threshold is <55% (figure not shown).

One way sensitivity analysis is conducted on the least cost-effective country setting (region Euro B). ICER estimates are robust against one-by one variation of all parameters except for genetic test cost (Table 4).

Table 3
Probabilities, utilities and 5-HTTLPR effect size.

	Distribution	Baseline	Sensitivity analysis LL−UL
Remission rate (no genetic test)°	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 (Euro A)*	Beta-PERT	0.12	0.08–0.19
Hospitalization rate (Euro B)*	Beta-PERT	0.80	0.70–1.0
Hospitalization rate (Euro C)*	Beta-PERT	0.60	0.50–0.80
Utility for acute depression °	Beta	0.40	0.30–0.60
Utility for remitted depression°	Beta	0.88	0.80–1.00
Treatment disutilities°	Beta	0.04	0–0.06
5-HTTLPR effect on ADR (OR)***	Log-normal	2.37	1.40–3.58
5-HTTLPR effect on AE (OR)***	Log-normal	2.31	1.40–3.50

°Beta 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., 2006a); Remission rate variation range (Cuffel et al., 2003) utilities/disutilities (Revicki and Wood, 1998);
*Beta-PERT. The LL and UL were drawn from literature-sources (region Euro A) (Banks et al., 1998). As for Eastern Europe countries (Euro B; C), the LL and UL were estimated by two authors (PO; AS) based on official sources [OECD, 2009 #3]. The baseline value, equal to mode, was calculated as follows: mode = min + (max − min)/3 (Golenko-Ginzbug, 1988).
**Beta-PERT. 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).
***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. Antidepressant response (ADR): meta-analysis (Serretti et al., 2007). Adverse effect burden (AE): STAR*D sample (Hu et al., 2007).

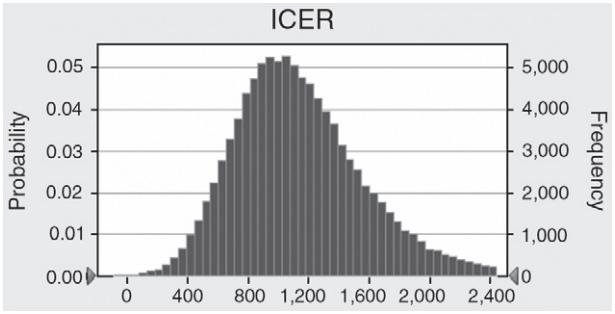

Fig. 1. Region Euro A. ICER range (10–90 percentile): $638–$1738; Mean ICER: $1155; Median ICER: $1095; Base-case ICER: between 40 and 50 percentile.

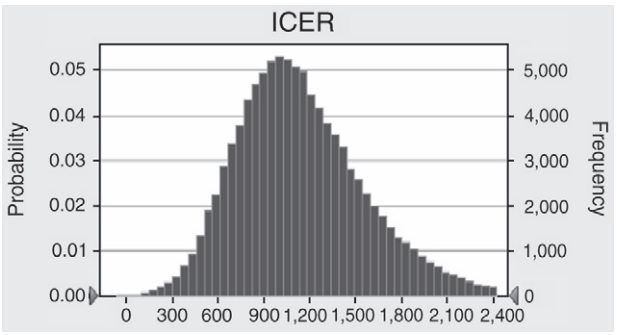

Fig. 3. Region Euro C. ICER range (10–90 percentile): $646–$1736; Mean ICER: $1157; Median ICER:$1099. Base-case ICER: between 40 and 50 percentile.

3.3. Verification scenario

Algorithm C (citalopram + bupropion administered to s/s carriers) is compared to algorithm A in region Euro A. Algorithm C incremental cost is $173. ICER is $1107.

4. Discussion

Pharmacogenetic studies have pointed to a large number of candidate genes that can modulate antidepressant response. Most genes are not supported by consistent evidence. For those that have emerged as sufficiently strong factors (e.g. the 5-HTTLPR polymorphism) (Serretti et al., 2007), researchers have often concluded that such genetic data will revolutionize the treatment of depression in the next few years. Notwithstanding this statement, no experimental data are available to quantify what increase in antidepressant response could be achieved by incorporating genetic profile to choose antidepressant drug. This is a substantial lack of information, which is only provisionally covered by simulated analyses. Smits et al. (2007) estimated theoretical gain in response to citalopram treatment if the choice of this or an alternative non-SSRI agent was based on 5-HTTLPR genetic test. They considered a short time horizon and used data from a randomized trial, while there was no economic evaluation. Perlis et al. (2009) performed a cost-utility analysis based on the Sequenced Treatment Alternatives to Relieve Depression study. Costs and quality-adjusted life years (QALYs) were compared for sequential antidepressant trials, with or without guidance from a pharmacogenetic test (5-HT2A polymorphism) for differential response to SSRIs. In a simulated scenario, likely SSRI responders received an SSRI, likely nonresponders were prescribed the norepinephrine/dopamine reuptake inhibitor bupropion. Economic evaluation (inpatient treatment; outpatient visits; drugs) was based on U.S. costs. Time-horizon for cost-effectiveness analysis was three years. Authors concluded that a benefit was present but only under certain circumstances. We already debated the weaknesses of this study such as longer follow up to reflect 'real world' treatment conditions and sequential approach to antidepressant choice (Serretti et al., 2011). Moreover it considered genetic control on antidepressant response but not on side-effects. To overcome these limitations, we implemented a decision analytic model that incorporates a short-term evaluation of costs and benefits in recurrent depressive episodes instead of following the patients for several months after remission and pooled pharmacogenetic effect on antidepressant response and tolerability (Serretti et al., 2011). This model, originally developed in Italian mental health setting, is currently applied, with some modifications, to three European regions at different economical development level. In East Europe (regions Euro B and Euro C) a larger proportion of individuals are treated in inpatient facilities, thus overall treatment costs are higher than in Western Europe, although costs for single services (hospitalization; outpatient visits; drugs) are lower. Despite this, we found almost the same incremental cost for pharmacogenetic approach in all Euro regions. In other words, the different use of inpatient facilities in Western and Eastern Europe does not appear to have a significant impact on economic evaluation. It is arguable that reduction in health expenditure for approximately 4% of new responders under pharmacogenetic treatment cannot offset incremental cost for genetic test. This lets critical factor be how much society would pay for more health and quality of life, which typically implies a cost-effectiveness threshold proportionate to economical level of the country. The World Health Organization uses GDP per capita to classify an intervention as very cost-effective, if ICER is

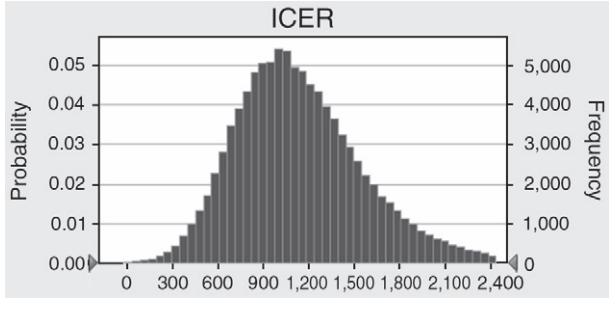

Fig. 2. Region Euro B. ICER range (10–90 percentile): $644–$1736; Mean ICER: $1156; Median ICER: $1097. Base-case ICER: between 40 and 50 percentile.

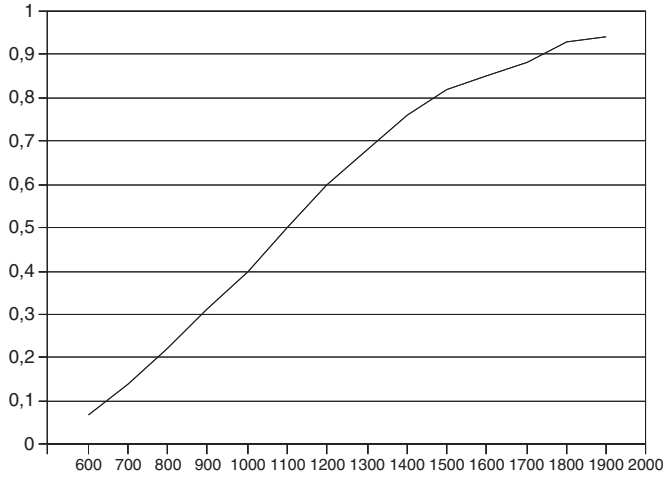

Fig. 4. CEAC (Region Euro A). CEAC shows the probability (axis Y) that ICER value falls below an established threshold (axis X). The World Health Organization suggests two cost-effectiveness thresholds: 1 GDP (per capita) (Euro A: $642 per week) and 3 × GDP (Euro A: $1926 per week). The probability of having and ICER value below the lower threshold is approximately 10% (very cost-effective). Instead the probability that ICER falls below the upper threshold is >90% (moderately cost-effective) (see discussion).

Table 4
ICER variation in region Euro B (least cost-effective setting).

	ICER
Hospitalization rate	$1185–$1185
Days in hospital	$1185–$1185
Cost of one visit	$1185–$1185
Cost of one day spent in hospital	$1185–$1185
Cost of bupropion	$1217–$1185
Cost of citalopram	$1185–$1187
Cost of genetic test[a]	$541–$1821

Variation ranges are reported in previous tables.
[a] Modeling variation in genetic test cost results in an ICER value that is below cost-effectiveness threshold (see Discussion).

inferior or equal to GDP per capita, or moderately cost-effective, if ICER is below 3 times GDP per capita (http://www.who.int/choice/en/). Our simulation suggests that using the results of 5-HTTLPR genetic test to start antidepressant treatment with a serotonin reuptake inhibitor or an alternative agent might be moderately cost-effective in high-income countries, considering 3 GDP per capita threshold. The probability of having an ICER value below 3 GDP threshold was found to exceed 90% in Euro A region. Conversely this probability was <30% in Euro B region and <55% in Euro C region, not favorable to use pharmacogenetic approach in middle-income countries. The World Health Organization uses disability-averted time units (DALE) to assess the benefit of treatment strategies. This measure, unlike quality-adjusted time (QALE), is conditional upon the patients' age. Although DALE and QALE are different concepts based on a disability-oriented and a health-oriented perspective, the two measures may produce similar results when fixed-reference ages are used (Airoldi and Morton, 2009). WHO GDP per capita threshold was recently applied to a study which assessed the cost-effectiveness of psychotherapy in recurrent major depression in a developing African country (Siskind et al., 2008). Benefit measure was still quality-adjusted time. Our cost-utility model was robust against variations in all parameters except for genetic test cost, that only produced the greatest changes in ICER. This role of genetic test as main cost determinant was also documented in previous studies (Perlis et al., 2009). Genetic test cost can vary widely across laboratories. Reimburse procedures are different in European countries, although public sector is more often involved. The cost of tests is well established in some western countries (e.g. UK), whereas little is known about fees in eastern Europe. We reasonably assumed an additional $200 for each patient's genotyping (Stallings et al., 2006) and a narrow variation range (Shaw and Zachr, 2002). This estimate was consistent with the cost of single SNP tests. For example Apolipoprotein E genetic test is currently offered at $150 (www.spectracell.com). So, until genetic analysis is an expensive procedure, its applicability is limited to the richest areas in Eurozone. This 'geographically' selective cost-effectiveness is common to other interventions. The World Health Organization compared a variety of interventions for depressive disorder across 14 economically homogeneous regions and found substantial interregional differences in cost-effectiveness (Chisholm et al., 2004). In this study second generation antidepressants, which are more expensive than TCAs, were found to be cost-effective in high- but not middle-income countries. TCAs were more cost-effective in developing nations. Minimum genetic test cost was set equal to $100, according to speculations that a single SNP test might not be less costly in the future (Wedlund and de Leon, 2001). With this lowest estimate, pharmacogenetic approach is also cost-effective in middle-income countries (Euro B region). The point in our simulation is that antidepressant drugs of which serotonin reuptake inhibition does not represent the only or primary pharmacodynamic mechanism might be insensitive to 5-HTTLPR modulation and produce the same response in all 5-HTTLPR genotypes. These agents might perform better than SSRIs in individuals with the s/s genotype (Serretti et al., 2011; Smits et al., 2007). Bupropion is one such drugs but similar considerations virtually hold for SNRIs, mirtazapine or TCAs. This hypothesis, central to the architecture of our model, is supported by a variety of studies (Huezo-Diaz et al., 2009; Min et al., 2009; Pollock et al., 2000) but it cannot be considered an established finding. An apparent contrast is that variation in the 5-HTTLPR affected antidepressant response to venlafaxine (Lee et al., 2010) and mirtazapine (Kang et al., 2007). Venlafaxine, however, was administered at lower doses (75–150 mg/d) that are consistent with a prominent serotonergic effect (Debonnel et al., 2007). TCAs are still a valid alternative to SSRI treatment in depressive disorders (Cipriani et al., 2011) and a cost-effective solution in developing nations (Chisholm et al., 2004). TCA prescription averages 6%–8% in European centers but in some countries such as Germany up to one quarter of depressed patients are treated with a TCA (Bauer et al., 2008). If such findings support the inclusion of TCAs in our simulation, it is a contraindication that TCAs have a less favorable profile than SSRIs in terms of side-effect burden and dropout rates (Barbui et al., 2007). This could bias the appraisal of benefits eventually deriving from pharmacogenetic approach. For all this, we selected bupropion as alternative to SSRI treatment. Bupropion is not commonly prescribed in Europe (Bauer et al., 2008) and in the United States (Milea et al., 2010). Most clinicians associate bupropion to SSRIs. Although this solution was successfully used to improve response in SSRI-resistant depression (Trivedi et al., 2006), its results are comparable to switching to bupropion after the failure of SSRI treatment (Rush et al., 2006b). Recent lines of evidence demonstrate that bupropion monotherapy dominates combined treatment in cost–utility terms (Leelahanai, 2010). Therefore we assumed bupropion monotherapy as preferential treatment for s/s genotype carriers (algorithm B) and tested bupropion-citalopram association as a verification approach more adherent to current practice. Both scenarios confirmed the superiority of pharmacogenetic approach in high-income countries. Our model is conservative and close to real-world conditions. (Serretti et al., 2011). However it has oversimplifications. It assumes that 5-HTTLPR variants have the same distribution and effect size in all European countries. Although Europe is considered to be the most genetically homogeneous continent, some patterns of genes are discernible and identified population groups. In his pioneeristic works, Cavalli Sforza described five clines of genes in Europe (Cavalli-Sforza and Piazza, 1993). Subsequent studies confirmed genetic stratification according to a principal north-southeast gradient and to a secondary west–east axis (Francois et al., 2010; Nelis et al., 2009). The influence of 5-HTTLPR on SSRI response is documented in randomized trials, but biased by various limitations (Serretti et al., 2007), whereas less clear evidence comes from naturalistic studies (Mrazek et al., 2009). We posited that sensitivity to 5-HTTLPR variants was equivalent for all SSRIs and determined it from meta-analytic data. However recent studies emphasize subtle differences between individual SSRI drugs (Kato et al., 2005). Since the individual clinical value of single SNPs is limited, attempts have been made to combine genetic information in the development of clinically useful genetic prediction tests. Thus, serotonin-related genes have shown to influence short-term antidepressant response in an interactive manner (Lin et al., 2009; Serretti et al., 2004). A recent study showed, using anatomical neuroimaging techniques in a sample of healthy subjects, that the BDNF MET allele was protective against 5-HTTLPR s allele-induced effects on a brain circuitry encompassing the amygdala and the subgenual portion of the anterior cingulate. These data provided in vivo evidence of biologic epistasis between 5-HTTLPR and BDNF. Significant improvement in understanding gene–gene interactions is expected from the widespread use of pharmacogenomics. Recently, genomewide association studies identified new polymorphisms which may modulate antidepressant response (Garriock et al., 2010; Wong et al., 2004). Gene–environment interactions may also play a substantial role in the fields of pharmacogenetics. Accordingly, serotonin transporter gene variants and live events have shown interacting effects on predicting response to SSRI drugs (Keers et al., 2011). Recent discoveries have changed the structure and function of the 5-HTTLPR polymorphism. Hu et al. (2006) reported on a SNP

(rs25531, A/G) in the Long form of 5HTTLPR that might have functional significance: the more common LA allele was associated with higher basal activity, whereas the less common LG allele had transcriptional activity no greater than the s-allele. These investigators suggested that in tests of association the LG alleles should be analyzed along with the s-alleles. 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 LA 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. Such findings might revolutionize 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, managed care and psychotherapy.

5. Conclusion

In conclusion, using principles and methodology of the World Health Organization, this cost-utility analysis demonstrates that introducing a preliminary genetic test to guide pharmacological treatment of major depressive disorder may be a cost-effective solution in high-income countries of Western Europe but not in middle-income countries of Eastern part. This difference reflects cost for genetic analysis. If this cost is going to decrease in the next few years, although it remains within a likely range, pharmacogenetic approach may become cost-effective in middle-income countries. This has implications for commercial strategies by manufacturers and for health policies by national governments.

Conflict of interests

None

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