Challenging sequential approach to treatment resistant depression: Cost-utility analysis based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial

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Abstract

In major depression, when a first antidepressant does not cause remission of symptoms (60%–75%), there are several options for continuing treatment in the next step. This study is a cost-utility analysis (CUA) of different second-line approaches. In a simulated trial outpatients with MDD were treated with citalopram for 13 weeks (level 1), then based on two alternative algorithms implemented from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Algorithm A: citalopram was continued until study endpoint (week 26). Algorithm B: patients who remitted during level 1 continued citalopram. Those who did not remit could opt for switching to another antidepressant (venlafaxine; sertraline) (b1) or adding bupropion to citalopram treatment (augmentation; b2). Algorithm B increased remission rate by 10.6% over Algorithm A (number needed to treat: 9.9; sensitivity range: 9.1–12.5). As a comparison, differences between active antidepressants and placebo are associated with NNT values of 6 to 8. In CUA Algorithm B was dominant with an ICER of $11,813 (sensitivity range= $1783 – $21,784), which is <1 GDP per capita cost-effectiveness threshold (USA=$47,193). Among Algorithm B options, switching (b1) dominated Algorithm A with a smaller number of responders than augmentation approach (b2) (NNT 11 vs. 7.7), whereas ICER values were similar (b1: $14,738; b2: $15,458). However we cannot exclude a bias in selecting second treatment. This cost-utility analysis shows (in line with current guidelines) a benefit in modifying

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1. Introduction

1.1. Burden related to major depression and response to treatment

Major depressive disorder (MDD) is the most common mental disorder, affecting approximately 1 in 5 adults worldwide, and the fourth major cause of disability (Ustun et al., 2004). Societal costs are considerable in terms of health expenditure (Watkins et al., 2009) and work days lost (Bender and Farvolden, 2008; Rytsala et al., 2005). Moreover depressed patients are characterized by health-related quality of life 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). Antidepressant drugs not only treat depressive manifestations but they can also improve quality of life (Llorca and Fernandez, 2007; Sarnes and Frankum, 2004). Nevertheless only 25–40% of patients on pharmacological treatment achieve full remission of symptoms in real world conditions (Cuffel et al., 2003), whereas 60–75% of them do not reach ideal treatment outcome.

1.2. Sequential approach to treatment resistant depression

Current guidelines are made to change antidepressant treatment if there is no adequate response after 6–8 weeks (American Psychiatric Association Practice Guidelines. Available at http://psychiatryonline.org). In the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (www.star-d.org), that was funded by the NIMH, the patients completed 13 weeks on a treatment regimen. If they failed to achieve remission within this cycle, their treatment was modified and they entered another cycle. At the end of four sequenced cycles approximately two thirds of the STAR*D sample remitted (Rush et al., 2006). This was used to support sequential approach to treat resistant depression. However in the STAR*D sample most patients responded after 6 weeks of treatment. Similarly delayed response was the most common pattern of antidepressant response in the large GENDEP study (Uher et al., 2011). In long-term antidepressant trials, responding to treatment within the first 2 months was associated with a greater probability of achieving remission after 6 months (Wade et al., 2009). Another study demonstrates that remission rate during SSRI treatment increases from week 8 to week 52 (Wade et al., 2006). This body of evidence suggests that in some depressed patients symptoms might decrease slowly and improvements occur long after three months of treatment. In addition since Kraepelin's era it has been acknowledged that major depression is a recurrent disorder and it is possible to recover from an episode within 6–8 months without treatment (Fox, 2002). Although sponta

neous remissions are more likely in the first weeks of depression (Posternak et al., 2006), there could be a substantial increase in such cases months later by effect of their accumulation over time. Thus if the patient under goes sequenced trials, each lasting a few months, increase in remission is not necessarily due to treatment change but it might reflect the spontaneous course of depressive episode towards recovery.

1.3. Objectives of cost-utility analysis

In this study we compared the first two steps of STAR*D to an alternative scenario, not implemented in STAR*D, in which patients with MDD were treated with the same SSRI for 26 weeks. This accounted for delayed response to antidepressant treatment and spontaneous remission, albeit estimated in a theoretical way. We performed a cost-utility analysis (CUA) on these scenarios. Secondly we compared switching and augmentation arms of STAR*D.

2. Experimental procedures

2.1. Sample and setting

The sample was made by STAR*D cohort of about 3000 adult outpatients (age 18–75 years) with major depressive disorder. Diagnostic assessment was performed by the treating physician using a non-structured interview and confirmed by a DSM IV based checklist. Exclusion criteria were indications for hospital treatment such as psychotic symptoms, suicidal risk or inpatient detoxification for alcohol/substance dependence. Women who were pregnant or breastfeeding were also excluded. Obsessive compulsive disorder and eating disorder require different treatment options, therefore these comorbidities were also reasons for no inclusion. The severity of depressive symptoms was assessed by the 17-item version of the Hamilton Rating Scale for Depression (HAMD17). A score greater than or equal to 14 was required for inclusion. The cohort's characteristics are reported in Table 1. The STAR*D was a chronic depressive sample. The mean duration of a depressive episode was 150 weeks. Patients were treated in primary care centers (PCC) or community-based mental health centers (CMHC) in the United States.

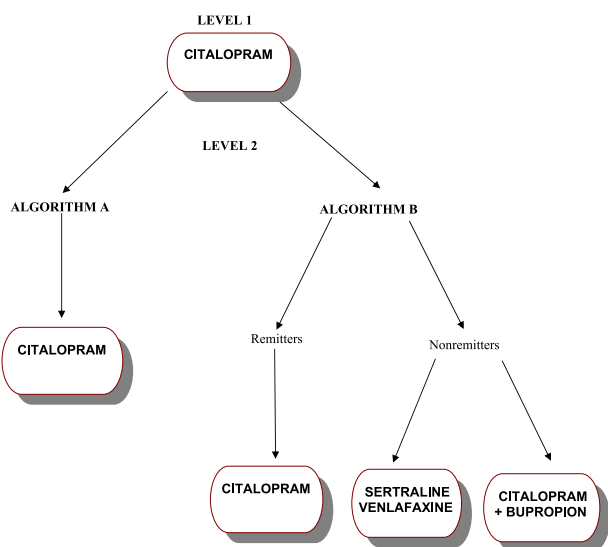### 2.2. Pharmacological treatment decision tree

Our STAR*D based decision tree (Rush et al., 2006) included two treatment levels (see Figure 1).

2.2.1. Level 1
All patients were treated with citalopram for 13 weeks. The starting dose was 10 mg/d. Citalopram was titrated to reach the target dose (40 mg/d) within 4 weeks. Citalopram was lowered by 10 mg/d if there were side-effects. Conversely the citalopram dose was increased to 50 mg/d if there was no partial response (HAMD decrease $<25\%$). Average citalopram dose was 41.8 ± 16.8 mg per diem.

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		0.75
Number of episodes	6.0 ± 11.4	
Length of illness (yrs)	15.5 ± 3.2	
Length of current episode (mos)	24.6 ± 51.7	
Axis I comorbidity		0.35

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

Figure 1 Pharmacological treatment. All patients were treated with citalopram for 13 weeks (level 1). Then two algorithms were implemented for subsequent 13 weeks: Algorithm A: level 1 treatment was continued until endpoint. Algorithm B: the patients who achieved remission within level 1 continued with citalopram—the others could opt for switching to sertraline/venlafaxine (b1) or adding bupropion to citalopram treatment (b2).

2.2.2. Level 2
This level was available for patients who completed level 1. Two alternative scenarios or algorithms were implemented for this 13-week lasting level.

Algorithm A. All patients included in level 2, both remitters and those who did not remit during level 1, were treated with citalopram for a further 13 weeks.

Algorithm B. Patients who were in remission (HAMD<7) at level 2 intake remained on citalopram until endpoint. Instead those who were not in remission were allowed to choose their next treatment according to an equipoise design. They opted for either treatment arm:

b1 (switch): citalopram was stopped; each patient was randomized to receive sertraline (100–200 mg/d: mean 135 mg) or venlafaxine (150–300 mg/d: mean 193 mg);

b2 (augmentation): citalopram was continued as in level 1; bupropion (150–300 mg/d: mean 267 mg) was added to SSRI treatment. Based on STAR*D results we projected that 58% of the cohort would switch therapy and 42% would choose augmentation (Rush et al., 2006).

2.3. Outpatient visits

The frequency of visits, established according to published guidelines (CG90 Depression in adults: NICE guidelines. Available at http://guidance.nice.org.uk) and similar to psychiatric practice in the United States, was once every 2 weeks in the first 3 months. In subsequent months the frequency ranged from once every 2 weeks in non-responders to once a month in those who achieved remission. The patients were visited by a physician. The first visit, aimed at a thorough diagnostic assessment, lasted approximately 1 h. Subsequent visits, in which the physician briefly assessed depressive symptoms and side effects related to medications, lasted 20 min.

2.4. Costs

We analyzed direct costs for drug acquisition and delivery and costs for visits in outpatient services Table 2. Information on drug prices was collected from Red Book (http://sites.truvenhealth.com/redbook) (average wholesale prices AWP; 20% discount applied to government institutions). Cost for outpatient care was based on World Health Organization data (WHO-CHOICE project. www.who.int/choice/en/). Community mental health centers were assumed to be equivalent to primary care centers. So the estimated cost for outpatient visit is similar to cost reimbursed by Medicare program that is approximately 60% of psychiatric visit fees. Cost data were referred to 2011. Costs for outpatient visits were available for 2008. They were adjusted to 2011 costs using OECD data (http://stats.oecd.org/) on average annual inflation in the 3 year period: United States, 1.5%. Indirect costs related to productivity loss were not included in CUA, as recommended in the guidelines for pharmacoeconomic analysis (Weinstein et al., 1996). In fact they were likely to be captured in the utility weights assigned to patients of depressive state, and would therefore be double counted if included as costs as well (Table 2).

2.5. Markov model and utilities

The Markov approach is often used to predict the probability distribution of a certain variable (i.e. disease progression) in a multi-state model. The model requires the knowledge or the estimation of the probabilities of transition for each change of state. Given the distribution of the initial state, each of the next states' probability distribution is obtained via a transition matrix that is the structure of the conditional probabilities. As an important assumption, Markov property states that the conditional probabilities at future steps depend univocally on the current and not on the previous states. When a model is applied to medical decision making, a disease course is divided into distinct states; transitions probabilities are assigned for movement between these states over a discrete time period (Markov cycle). By attaching estimates of resource use and health outcome consequence to states and transitions in the model, then running it over a number of cycles, it is possible to estimate long-term costs and outcomes associated with a disease and a particular health intervention. In this study a Markov model was developed in Microsoft Excel to analyze transitions from depression to remission state, and from remission and nonremission to drop out state. Dropout patients either remitted or continued to be in depression. Remitting patients

Table 2 Direct Costs (USD, 2011).

	Baseline	Range	Sources
Drugs (3 months)			
Citalopram (41.7 mg/d)	193	96-289	AWP (Red Book)
Bupropion (267 mg/d)	354	177-531	AWP (Red Book)
Venlafaxine (193 mg/d)	375	187-561	AWP (Red Book)
Sertraline (135 mg/d)	304	152-456	AWP (Red Book)
Outpatient visit	55	27.5-82.5	World Health Organization (WHO-CHOICE project)
ICER thresholds based on gross domestic product (GDP) per capita (WHO-CHOICE methodology)			
Very cost-effective (<1GDP per capita)	47,193		
Cost-effective (<3GDP per capita)	141,179		

AWP (average wholesale price) refers to the average value at which wholesalers sell drugs to physicians, pharmacies and other providers (USA). Red Book (http://sites.truvenhealth.com). WHO-CHOICE (Choosing Interventions that are Cost-Effective): a World Health Organization (WHO) initiative developed in 1998 with the objective of providing policy makers with cross-country data on cost-benefit of health interventions (http://www.who.int/choice/en/).
Incremental Cost-Effectiveness Ratio (ICER): (Cost B−Cost A)/(QALY B−QALY A), A=treatment A, B=treatment B, LL=lower limit, UL=upper limit, SE=standard error, SD=standard deviation.
All costs are expressed in US dollars (2011). Costs are normally distributed. Mean is set equal to the baseline value. The lower limit (LL) and upper limit (UL) of distribution, reported in brackets, are set to 0.5 times and 1.5 times the baseline value, respectively. Standard error (SE), equal to standard deviation, is calculated as follows: $SE=(UL\text{-}LL)/(1.96 \times 2)$.
Costs for visits are drawn from the WHO_CHOICE (see above) These costs, available for year 2008, are inflated by mean annual inflation rate observed in OECD countries during the period 2009-2011: United States: 1.5% (total increase: 4.5%).
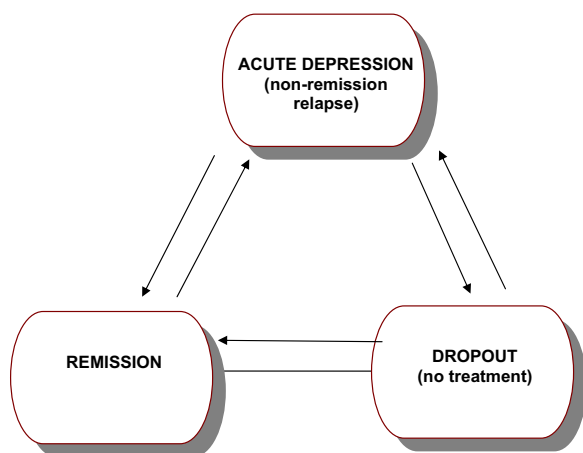
Figure 2 Markov model states. This figure shows Markov states and represented transitions from one state to another (arrows) in a Markov cycle. Acute depression, non-remission and relapse were assigned the same utility score, thus they were represented as one state. Patients were initially in acute depression, then they could remit or remain depressed. Both remitting individuals and those who did not remit could drop out from treatment. Remitting patients (including those who had discontinued their treatment) could relapse.

could relapse. Relapse and nonremission were considered to be equal to acute depression (see Figure 2). Suicide was not represented. The structure of Markov model included four 6.5 weeks lasting cycles. We hypothesized that all patients were in acute depression within cycle 1. At the end of this cycle transitions occurred by effect of level 1 treatment, and the proportions of remitting, not remitting and dropout patients were not modified in cycles 2 and 3. Health state probabilities were expected to change

at the end of cycle 3 because of level 2 treatment. These probabilities were used to model cycle 4. For each cycle transition probabilities were included in a matrix, then cumulative probabilities across all cycles were estimated by performing matrix product. Probabilities were estimated from STAR*D and other published studies (see Table 3). Each health state was assigned a utility score to reflect the amount of quality of life attached to it. Utility scores were differentiated by health conditions and treatment-related conditions as follows (Revicki and Wood, 1998): acute depression, nonremission and relapse=0.4; remission=0.9; treatment-related burden=−0.04 (see Table 3).

2.6. Cost-utility analysis

Cost and utility data were processed along with Markov cycle transitions. This allowed the calculation of overall cost and quality-adjusted life years (QALY) associated with Algorithms A and B. The acceptability of the dominant algorithm was established in terms of incremental cost-effectiveness ratio (ICER), which is defined as the ratio of the change in costs of a therapeutic intervention, compared to the alternative, to the change in effects of the intervention, according to the formula: (Cost Algorithm B−Cost Algorithm A)/(QALY Algorithm B−QALY Algorithm A). A secondary analysis differentiated between switching arm (b1) and augmentation arm (b2) of Algorithm B, which were compared to Algorithm A. 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, number of outpatient visits and costs. Probabilities and utilities, which vary over a 0-1 range, should have beta-distribution (Andronis et al., 2009). Baseline values, estimated from literature and official sources (see above), were assumed to be the means of distributions. The lower and upper limits of variation ranges were established as reported in Table 3, similar to previous publications (Olgiati et al., 2012; Serretti et al., 2011). Probabilistic sensitivity analysis (Monte Carlo) accounted for interactions between the whole parameters and generated a probability distribution of ICER

Table 3 Probabilities (3 months) and utility scores.

	Baseline	Range	Sources
Probabilities			
Remission (level 1)	0.27	0.20-0.41	STAR*D (Rush et al., 2006)
Remission (level 2; Algorithm A)	0.07	0.05-0.09	52 weeks SSRI trial (Wade et al., 2006) In this sample remissions increased from 2.5% per week in the first eight weeks to 0.4% in subsequent weeks
Remission (level 2; Algorithm B)	0.30	0.23-0.45	STAR*D (Rush et al., 2006)
(algorithm b1)	0.27	0.21-0.33	STAR*D (Rush et al., 2006)
(algorithm b2)	0.35	0.26-0.53	STAR*D (Rush et al., 2006)
Remission (no treatment)	0.05	0.04-0.07	Prospective naturalistic study. Survival analysis of untreated depression (Posternak et al., 2006)
Dropout (level 1)	0.26	0.19-0.40	STAR*D (Warden et al., 2007)
Dropout (level 2)	0.23	0.17-0.35	STAR*D (Warden et al., 2009)
Relapse (treatment)	0.05	0.04-0.07	Model of depression implemented for cost-utility analysis (Perlis et al., 2009)
Relapse (no treatment)	0.13	0.10-0.19	Model of depression implemented for cost-utility analysis (Perlis et al., 2009)
Utility scores			
Acute depression / relapse	0.40	0.30-0.60	(Revicki and Wood, 1998)
Remitted depression	0.90	0.68-1.00	(Revicki and Wood, 1998)
Treatment-related disutility	0.04	0.03-0.06	(Revicki and Wood, 1998)

LL=lower limit, UL=upper limit, SE=standard error, SD=standard deviation.
Sensitivity analysis. Probabilities and utilities have beta distribution. Baseline value corresponds to the mean of distribution. The LL is set equal to 0.75 times the baseline value. The difference between the baseline value and the LL is assumed to be 1/3 the difference between the UL and LL (Golenko-Ginzburg, 1988). SE (equal to SD) is calculated as (UL-LL)/2 × 1.96. Slope parameters α and β are estimated as follows: mean=$\alpha/(\alpha+\beta)$ and SD= $\sqrt{(\alpha\beta)}/(\alpha+\beta)$ $(\alpha+\beta)$ (22).

values (of which mean, SD and 95%CI were reported). A few variables were interrelated as in naturalistic contexts: side-effect burden and the likelihood of discontinuing antidepressant treatment (Machado et al., 2006); patient's age and delayed (after 3 months) response to treatment (Driscoll et al., 2005); symptom severity at treatment intake and antidepressant response (Kirsch et al., 2008). 100,000 trials were run for simulation using the commercial software Crystal Ball by Oracle (www.oracle.com). One way sensitivity analysis was performed to identify which parameters could significantly affect cost-utility.

3. Results

3.1. Remission and dropout rates for control scenario (Algorithm A)

The cumulative rate of remission for control scenario, in which antidepressant treatment was unchanged for 26 weeks (Algorithm A), was equal to 34.6% and it varied from 33.7% to 36.5% based on sensitivity ranges reported in Table 3. Dropout rate was estimated to be 44.8%.

3.2. Remission and dropout rates for Algorithm B (b1 and b2)

The cumulative rate of remission for STAR*D based scenario, in which antidepressant treatment was changed for those not

remitting within 13 weeks (Algorithm B), was equal to 45.2%. This value was 10.6% greater than what was estimated for Algorithm A. The difference corresponded to a number needed to treat (NNT) of 9.9 when those algorithms were compared. Considering the lower and upper limits of remission achieved by applying Algorithm A as reported below, NNT varied from 9.1 to 12.5. Algorithm B dropout rate was 45%. Algorithm b1 (switching approach) was associated with a remission probability of 43.95%, which corresponded to a NNT of 11.2 compared to Algorithm A. Algorithm b2 (augmentation) was associated with a remission probability of 47.5% (NNT=7.7).

3.3. Cost-utility analysis

Algorithm B overall cost was $800.33. Incremental cost over Algorithm A was $75.92 necessary to produce 0.007 more QALYs. Based on these results, ICER was equal to $11,481. In probabilistic sensitivity analysis mean ICER value was $10,665±2,126 (95%CI: 6498-14,832). Utility scores assigned to depression and remission states and the probability of achieving remission after 3 months of treatment (Algorithm A) had the strongest impact on ICER variation. However these variables could not shift ICER value above 1 × GDP threshold (Table 4), which is suggested as a cost-effectiveness threshold (see discussion). Algorithm b1 produced 0.006 more QALYs than Algorithm A at an incremental cost of $84.74. This corresponded to an ICER of $14,738.

Table 4 One way sensitivity analysis.

	Range	ICER
Algorithm A remission	0.05-0.11	10,457-14,176
Utility for acute depression	0.30-0.60	9567-19,135
Utility for remitted depression	0.68-1.00	20,502-9568
Cost of citalopram	96.0-289	15,120-7842
Cost of bupropion	177-531	7162-15,800
Cost of venlafaxine	187-561	8322-14,640
Cost of sertraline	152-456	8920-14,042

Only factors that produce >$500 ICER variations over baseline value are reported.

The difference between algorithms b2 and A was 0.008 QALYs, whereas incremental cost was $124.44 (ICER= $15,458).

4. Discussion

4.1. Changing antidepressant treatment vs. leaving it unchanged

STAR*D is a pivotal study in the field of treatment resistant depression; however its greatest limitation is the lack of a control arm in which first-line antidepressant is maintained for several months compared to the existing level 2 steps. We integrated this scenario (Algorithm A) in a theoretical model and analyzed its findings as number needed to treat and cost-utility ratio. In clinical terms our simulation indicates that 9-12 individuals should have modified their antidepressant treatment if not remitting within 3 months to achieve one more remission than those remaining on the same treatment for 6 months. This is not consistent with a clear-cut difference favoring sequenced treatment approach to resistant depression as a NNT<10 was suggested as a threshold of clinical significance by the National Institute of Clinical Excellence, UK. Moreover NNT values of 6 to 8 were reported in SSRI-placebo comparisons [Thase, 2011 #224]. On the other hand even a small benefit in clinical response might be valuable for quality of life and subjective well being, and this might justify increased costs. In fact our analysis showed that changing antidepressant treatment would allow a gain of 0.007 QALYs at an incremental cost of 76$. This corresponds to $11,481 spent (ICER) to achieve one more QALY. This is an excellent result based on cost-effectiveness thresholds commonly in use. For example, the World Health Organization suggests gross domestic product (GDP) per capita as a reliable measure in cost-effectiveness studies (http://www.who.int/choice) Thus an intervention is dominant over the alternative one if ICER emerging from their comparison is below 1 GDP per capita, and it is still moderately cost-effective if ICER is between 1 and 3 GDP per capita. In the United States, GDP per capita was estimated to be $47,193 in 2011. (http://stats.oecd.org).

4.2. Changing strategies: switching vs. augmentation

Our simulation shows that switching to a different antidepressant medication if there is no remission within 13 weeks is associated with a smaller clinical benefit than taking the same antidepressant for the following weeks with the addition of another agent (NNT: 11 vs. 7.7). Switching strategy is less favorable, perhaps because the onset of antidepressant response continues over the first months of treatment but late response cannot be seen when the antidepressant is changed. So an antidepressant must be taken for a long period to maximize its therapeutic effects. These results echoed those of two studies on treatment resistant depression carried out at different university sites across Europe. In the first study no advantage was reported for switching to a different class of antidepressants instead of continuing on the same class (Souery et al., 2011a). In the second work switching from a SSRI to a TCA or vice versa was associated with a marginally worse outcome than staying on the same antidepressant (Souery et al., 2011b). However we note that in STAR*D the choice of delivering antidepressant treatment according to an equipoise design (patients were allowed to opt for their preferred solution) could have inflated the benefit of augmentation approach. Indeed patients with at least a moderate improvement on citalopram treatment were more likely to continue this medication.

4.3. Strengths and limitations of the model

We acknowledge that it is possible to remit from a major depressive episode after 3 months of treatment. In those who have not modified their treatment, remitting could be due to delayed onset response to antidepressant medication but also to spontaneous remission once treatment effect has disappeared. Spontaneous remission is dependent on the untreated period. It is approximately 10-20% after 3-6 months of illness and no treatment (Posternak and Miller, 2001; Whiteford et al., 2012); however the longer the depressive episode, the lower the probability of spontaneous remission (Whiteford et al., 2012). In our cohort the length of episode averaged 24 months and this suggested a low spontaneous remission. Late response to antidepressant treatment and spontaneous remission had modest effect sizes in our model, yet their impact was not negligible on remission rate. Therefore we included these data. Some characteristics of our study limit the generalization of its results. State transition model did not account for the risk of suicide. This was estimated to be 4/10,000 over a 6-month period (Simon et al., 2006). Acute depression before treatment and lack of remission during treatment were assigned the same utility score. This does not account for patients who fail to remit but partially respond to treatment. Nevertheless sensitivity analysis was performed on a wide utility range that should encompass both patients in acute depression and those who are not in remission but have an improvement in depressive symptoms. The study failed to document prior antidepressant treatments which, however, cannot be excluded. Some treatment choices based on STAR*D algorithms are relatively common in

psychiatric practice in the United States, but this is not warranted for other countries. In particular citalopram may not be an ideal first-line treatment for depression. A number of studies state that, for instance, escitalopram and venlafaxine are stronger antidepressants (Cipriani et al., 2007). STAR*D was a chronic depressive sample (length of current episode up to 150 weeks; length of illness 15 years; 75% recurrent depression) and in most patients there were other axis I disorders. Thus our findings might not be applicable to samples with different characteristics.

4.4. Conclusions

The results of this cost-utility analysis are consistent with current guidelines suggesting that antidepressant treatment should be modified after 3 months of insufficient response. However there might be less advantage for this approach than generally acknowledged, and it is necessary to combine symptomatic improvement, quality of life and costs to demonstrate its dominance over continuing with first-line treatment. Late response to antidepressant treatment, though modest, and the likelihood of spontaneous remission contribute to symptomatic outcome in acute phase treatment. Late response is common in elderly patients (Driscoll et al., 2005; Fischer et al., 2003). Spontaneous remission is more likely in the first weeks of depressive disorder, but it still occurs at a substantial rate in patients who have been depressed for 3–12 months (Posternak et al., 2006). In this group of patients who are early on treatment, but after 3 months of illness, and in elderly depressed patients any approach to treatment resistant depression should be compared with a control strategy of continuing one antidepressant for several weeks.

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Contributors

Alessandro Serretti designed the study and wrote the protocol. Paolo Olgiati developed the decision-analytic model and wrote the manuscript. Emanuele Bajo and Marco Bigelli performed economic analysis (Markov model and probabilistic sensitivity analysis). Stuart Montgomery reviewed the aims and method of the study. He improved the protocol by suggesting a control scenario, not implemented in the STAR+D study, in which first-line treatment was continued for the whole follow up period. All contributors critically read and approved the manuscript.

Conflict of interests

Dr. Serretti is or has been consultant/speaker for Abbott, Angelini, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Pfizer, Sanofi, Servier.

Professor Montgomery is or has been consultant/speaker for AstraZeneca, Bristol MyersSquibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Merz, Neurim,Pierre Fabre, Pfizer, Sanofi, Servier, Shire, Sepracor, Takeda, Targacept, Wyeth, Bionevia,M's Science, Otsuka, Pharmaneuroboost, Richter, Roche, Theracos, Transcept, UBC and Xytis.

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