Research paper

The cost-utility of stepped-care algorithms according to depression guideline recommendations – Results of a state-transition model analysis

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ABSTRACT

Background: Evidence-based clinical guidelines for major depressive disorder (MDD) recommend stepped-care strategies for sequencing evidence-based treatments conditional on treatment outcomes. This study aims to evaluate the cost-effectiveness of stepped care as recommended by the multidisciplinary clinical guideline vis-à-vis usual care in the Netherlands.

Methods: Guideline-congruent care as described in stepped-care algorithms for either mild MDD or moderate and severe MDD was compared with usual care in a health-economic state-transition simulation model. Incremental costs per QALY gained were estimated over five years from a healthcare perspective.

Results: For mild MDD, the cost-utility analysis showed a 67% likelihood of better health outcomes against lower costs, and 33% likelihood of better outcomes against higher costs, implying dominance of guideline-congruent stepped care. For moderate and severe MDD, the cost-utility analysis indicated a 67% likelihood of health gains at higher costs following the stepped-care approach and 33% likelihood of health gains at lower costs, with a mean ICER of about €3,200 per QALY gained. At a willingness to pay threshold of €20,000 per QALY, the stepped-care algorithms for both mild MDD and moderate or severe MDD is deemed cost-effective compared to usual care with a greater than 95% probability.

Limitations: The findings of our decision-analytic modelling are limited by the accuracy and availability of the underlying evidence. This hampers taking into account all individual differences relevant to optimise treatment to individual needs.

Conclusions: It is highly likely that guideline-congruent stepped care for MDD is cost-effective compared to usual care. Our findings support current guideline recommendations.

1. Introduction

Major depressive disorder (MDD) diminishes quality of life and is associated with functional impairment, which has a tremendous impact on individuals, their relatives and society. In view of its high prevalence, MDD is costly from both a health care and a societal perspective (Ferrari et al., 2013; Chisholm et al., 2016).

Stepped care service delivery can support decision making on gradually intensifying care according to patient's needs, while maximizing the overall benefit of resources. Interventions that are lower in intensity are preferred in treatment choices if adequate and acceptable, to avert overtreatment. The course of symptoms and change of need steers treatment through monitoring of treatment response and periodically evaluating care, to avert undertreatment. Controlled studies have
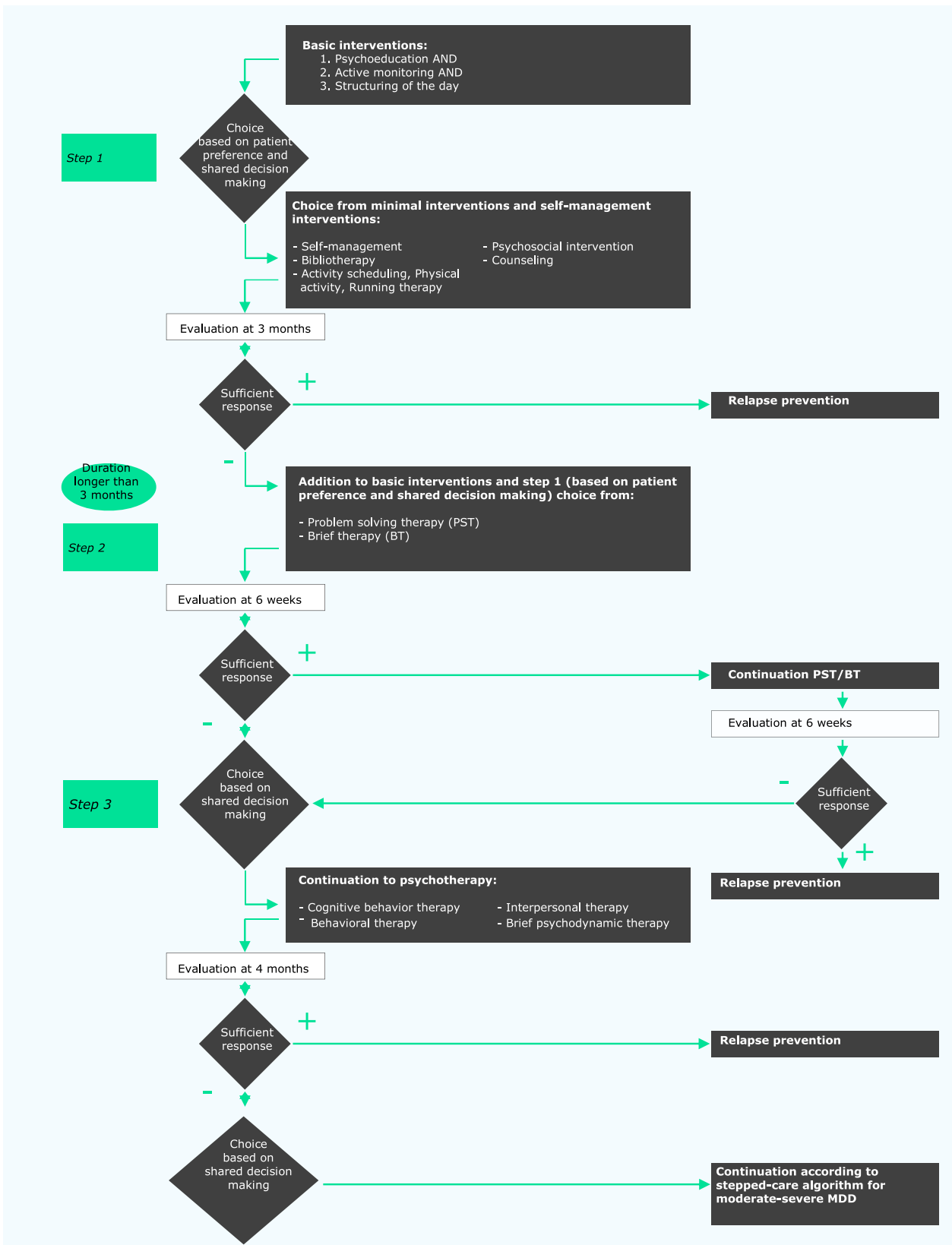
Fig. 1. Stepped-care algorithm for mild episodes of major depressive disorder.

Following the stepped-care algorithm for mild MDD starts with the basic and minimal interventions. At a duration longer than three months or a recurrent episode, the patient may choose to combine the basic interventions with either problem solving therapy (PST) or brief therapy (BT). When this step does not lead to sufficient treatment response a third step is indicated with psychotherapy (PT), which consists of (cognitive) behavioral therapy, interpersonal therapy, or brief psychodynamic therapy. When the third step does not lead to treatment response after four months, the guideline suggests to either switch to one of the other types of psychotherapy or to switch to antidepressants (AD). Insufficient response is indicated with a 'minus' sign; sufficient response is indicated with a 'plus' sign.
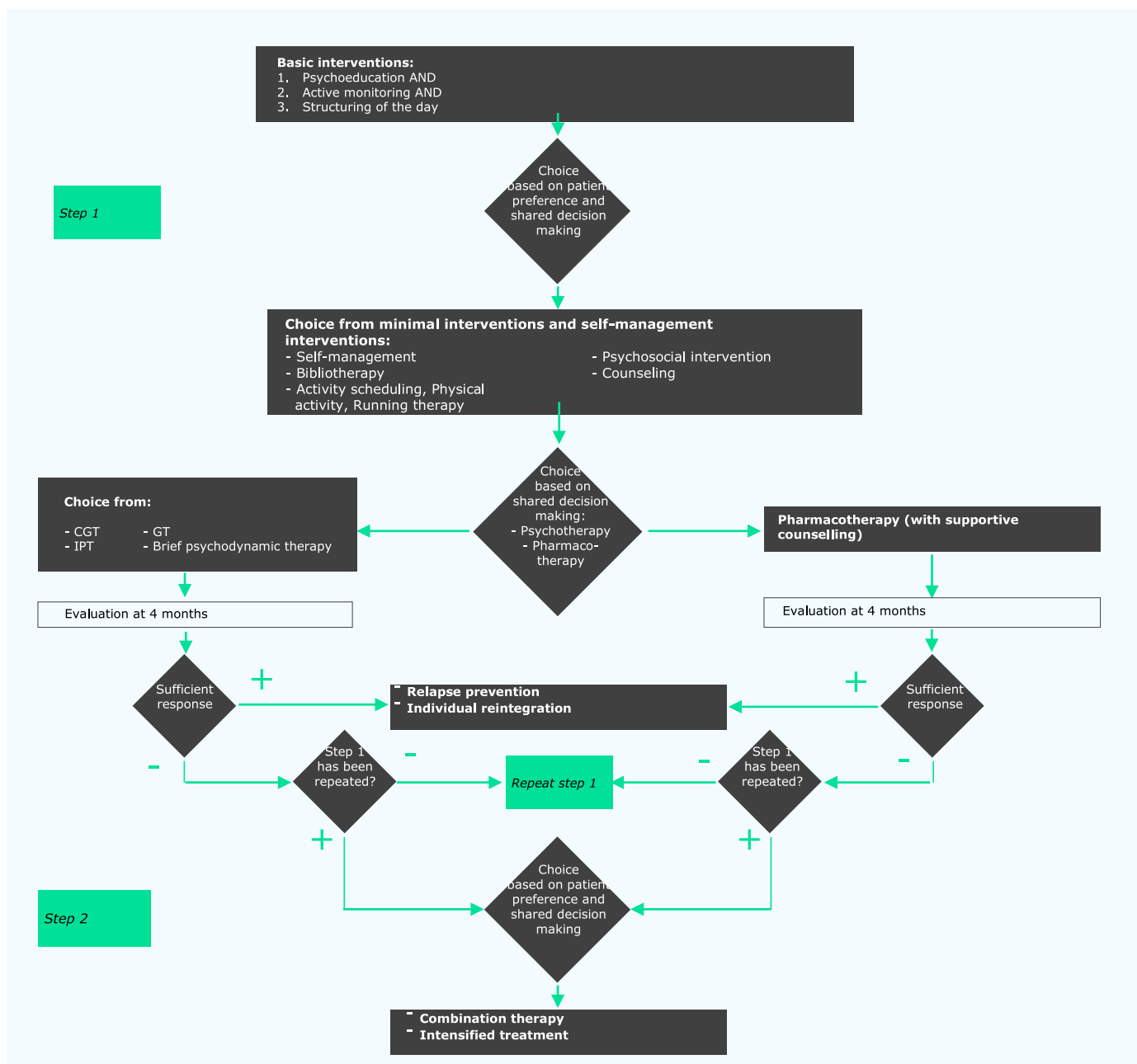
Fig. 2. Stepped-care algorithm for moderate-severe episodes of major depressive disorder.

According to the second algorithm, for single episodes of moderate and severe MDD, either psychotherapy or pharmacotherapy is immediately indicated in addition to the basic interventions, combined with minimal interventions according to the patients' preference. When this first step does not lead to a sufficient treatment response and in case of recurrent moderate or severe episodes of MDD, the guideline recommends to start treatment with either PT or combination therapy (PT and AD). The guideline deprecates pharmaceutical mono-therapy for these patients, because the longer-term prophylactic effect of psychological intervention protecting against recurrences would then be missed. Insufficient response is indicated with a 'minus' sign; sufficient response is indicated with a 'plus' sign.

demonstrated the clinical effectiveness of stepped care in general medicine and mental health and addiction care (Bower & Gilbody, 2005; Haaga, 2000). Clinical guidelines for depression recommend stepped-care strategies that sequence evidence-based treatment options and monitor outcomes (Spijker et al., 2013; Meeuwissen et al., 2008; NICE, 2018, Richards et al., 2012; NZGG, 2008). This allows tailoring treatment intensity to the patient's needs while accounting for treatment response (or the lack thereof) in previous and less intensive treatment steps. Studies on the clinical effectiveness of stepped care in depressed patients found small positive effects on depression outcomes (van Straten et al., 2015; Firth et al., 2015). Other effectiveness studies for sequenced treatment strategies have shown positive results as well

(van Dijk et al., 2015; Oosterbaan et al., 2013; van Orden et al., 2009; Trivedi et al., 2004). These studies showed that stepped-care interventions for depression are at least as effective as usual care, although current evidence is limited through methodological variety across studies. Although the evidence-base for the clinical effectiveness of stepped care for treating depression is growing, the evidence on cost-effectiveness of stepped care compared to care as usual is still limited (van Straten et al., 2015; Firth et al., 2015).

Insight into the cost-effectiveness of stepped care can help to optimise treatment allocation and improve the quality of care for depression in a cost-effective manner. This study employed a modelling approach to gain insight into the cost-effectiveness of stepped care, as

suggested by Bower & Gilbody (2005). The aim of this study is to evaluate the cost-utility of depression care when applying stepped-care algorithms according to the Dutch multidisciplinary guideline for depression (Spijker et al., 2013) in comparison to care as usual. This evidence-based guideline aims to reduce under-treatment as well as over-treatment and may therefore introduce health economic benefits that differ from usual care. Our hypothesis is that in stepped care health gains can be achieved cost-effectively, through either better outcomes or similar outcomes at reduced costs in the long run.

2. Methods

2.1. State-transition modelling approach

In this economic evaluation we have combined available evidence on clinical effectiveness and costs from different sources in a state-transition model. We used epidemiologic and clinical research data to take into account actual prevalences and severities to construct a representative clinical sample. We used clinical data to specify the percentage of each clinical subgroup that receives treatment and also the percentage that responds to treatment in each subgroup. Expert opinion was used to allocate patients to treatment. Next, we used effect sizes from meta-analyses to calculate how much improvement each clinical subgroup experiences from each type of treatment. Transitions across health states were modelled to assess the cost-utility (i.e. the health care costs per quality adjusted life year, QALY, gained) of guideline-based stepped-care scenarios for MDD compared to reference scenarios reflecting usual care.

2.2. Target population

The target population consists of adult patients in Dutch mental health care with mild, moderate or severe MDD without psychotic symptoms. In the Dutch population aged 18–64 years, 5.2% met the DSM-IV criteria for MDD in the last year, while the lifetime prevalence is 18.7% (de Graaf et al., 2010). This prevalence rate is comparable to other Western-European countries (Kessler et al., 2007).

2.3. Guideline-congruent care

The Dutch Multidisciplinary Guideline for Depression (third revision; Spijker et al., 2013) has been updated following the method of evidence-based guideline development, involving a large number of professional associations and patient participation. The developing and updating procedures are comparable to the methods and procedures of the National Institute for Health and Care Excellence (NICE, 2014; Philips et al., 2004). For the current clinical guideline, stepped-care algorithms were developed to support caregivers with sequential treatment allocation that takes into account the severity, course and duration of symptoms. There are basic interventions to be offered to all patients in both algorithms. These are psycho-education, active monitoring of symptoms and structuring of the day. Minimal interventions, including bibliotherapy or (online) self-management, may be added when the patient prefers to. According to the guideline, based on the diagnosis of either mild or moderate to severe MDD and the recognition of a recurrent episode, following the stepped-care algorithm for either mild MDD or moderate and severe MDD is indicated (See Figs. 1 and 2).

2.4. Comparator: care as usual

Care as usual (CAU) consists of all commonly available treatments in the health care system, often delivered in a mix of care. Guideline-congruent care is different from CAU in two ways: (a) basic interventions (i.e. psycho-education, active monitoring of symptoms, structuring of the day) are provided to all patients; and (b) the specific sequence and duration of evidence-based treatment interventions is made explicit. Treatment decisions are guided by observed treatment response such that patients who show no improvement at a certain time point are offered a next treatment step, often consisting of more intensive treatment.

2.5. Stepped-care scenarios and reference scenarios

We constructed two guideline-congruent stepped-care scenarios based on the algorithms in the Dutch Multidisciplinary Guideline for Depression, one for mild MDD, and another for moderate and severe MDD, as well as their CAU-reference scenarios. The number of patients reached per intervention, initially or after stepping up for patients who needed this (since insufficient effect was reached with previous treatment for any reason), was based on expert opinion of members of the guideline development group, informed by literature review. Effect sizes of the interventions in guideline-congruent care to establish the effect on quality of life were obtained from literature reviews on effectiveness of each of the distinct interventions, as described in the evidence-based guideline. The stepped-care scenarios describe the resource use and accompanying effects on quality of life that will differ from usual care.

For comparison we described and valued CAU-reference scenarios based on a selection of large empirical databases from the Netherlands. Population-based cohort data were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS; Spijker et al., 2002; Kruijshaar et al., 2005; Smit et al., 2006; Cuijpers et al., 2007a). Empirical data on the use of care in the Netherlands Information Network of General Practice (LINH) database of longitudinal data on prescribing and referral by general practitioners and in the Second National Survey of General Practice study were used (Nuyen et al., 2008; Braspenning et al., 2004; SFK, 2007; CVZ, 2008; Gardarsdottir et al., 2007). Data were also derived from the control arms of clinical trials that measured the costs associated with depressive disorder for at least one year as well as empirical studies with a distribution of mild versus moderate and severe MDD (Bosmans et al., 2008; Stant et al., 2008; van Roijen et al., 2006).

For each scenario, input parameters are the treatment interventions offered, the coverage as a percentage of patients of the target population, the effectiveness of the treatment interventions (in the stepped-care scenarios) or the mean value for quality of life (in the CAU-reference scenarios) and the estimated costs of care consumption. The coverage rates, (effect on) quality of life and costs estimates of the care consumption per scenario are described in the Results section.

2.6. The health-economic simulation model

The health-economic model compares the guideline-congruent stepped-care scenarios with the CAU-reference scenarios. This depression state-transition model simulates the health and economic impacts of interventions for varying depression severity levels. The state-transition model is suited to our study as it conceptualizes the course of depression in terms of health states (at risk for depression, mild MDD, moderate and severe MDD, recovery from mild MDD and recovery from moderate and severe MDD) along with the probabilities of making transitions across these states including time dependent parameters leading to valid estimations for the compared scenarios (Siebert et al., 2012). The model was based on Van Baal et al. (2008) and has been applied in other studies (Mohseninejad et al., 2013; Berg et al., 2011). Van Baal and colleagues based their model on an established Australian model by Vos et al. (2005) and adapted it to the Dutch setting. For the purposes of our study, Van Baal's model was adapted to distinguish between mild MDD versus moderate and severe MDD and the corresponding transition probabilities between the health states. The model was further adapted to accommodate the various treatment scenarios. The structure of the depression state-transition model is depicted in Fig. 3. A cycle of four weeks is applied (0–4 weeks, 5–8 weeks, etc.),
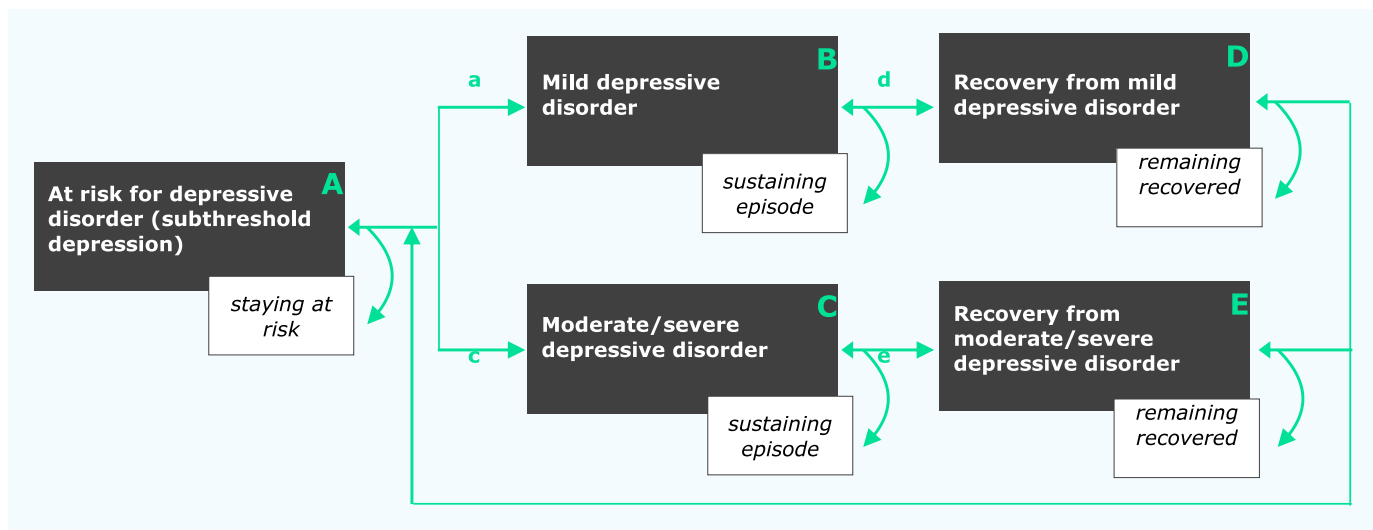
Fig. 3. Structure of the depression state-transition model.

A person at risk for depression (state A) either stays in this state or develops a major depressive disorder (MDD) (states B or C). A person with an episode of mild depressive disorder (state B) either stays in this condition, recovers from this condition (state D). A person with an episode of moderate or severe depressive disorder (state C) either stays in this condition or recovers from this condition (state E). After recovery from a depressive disorder (state D or E) a person either stays in this state or has a recurrence (state B or C).

Transition rate 'a' is the probability of moving from being 'at risk' for depression (state A) to state B, a mild MDD; 'c' is the transition rate from being at risk for depression (state A) to moderate and severe MDD (state C); 'd' is the recovery rate from mild depressive disorder; 'e' is the recovery rate from moderate and severe depressive disorder.

Textbox 1
Assumptions and justifications of the depression state-transition model.

Assumption	Justification
The depression state-transition model distinguishes mild major depressive disorder from moderate or severe major depressive disorder.	In the classification of (major) depressive disorder (MDD) the depression severity can be specified as mild, moderate or severe (APA, 2013). For moderate and severe depressive episodes, treatment following the same algorithm is recommended (Spijker et al., 2013).
A cycle of four weeks is applied (0–4 weeks, 5–8 weeks, etc.), allowing a transition to another health state in every four weeks.	The cycle length is short enough to simulate the frequency of clinical events and treatment interventions (Siebert et al., 2012). Longer cycles introduce more bias (Chhatwal et al., 2014).
The probability to recover declines as the length of the episode increases. The probability to have a relapse or recurrence decreases over time since recovery.	The probability of recovery is decreasing as the length of the depressive episode increases (Spijker et al., 2002; Bockting et al., 2006). Recovery as a function of disease duration and relapse rates as a function of time since recovery were estimated on the NEMESIS study and an Australian modelling study (van der Werf et al, 2006; Vos et al., 2004), as described in Berg et al. (2011).
We conservatively assume that treatment according to guideline recommendations does not result in a significantly faster recovery or lower chance of relapse or recurrence than care as usual.	The outcomes of treatment options can be split into (1) a direct effect, when the quality of life during a depressive episode improves as the number or severity of symptoms diminish; (2) an effect on recovery, when the duration of a depressive episode or the time to recovery shortens; and (3) an effect on relapse, when the probability of relapsing into a new episode of depression decreases. However, in the Dutch Multidisciplinary Guideline for Depression (Spijker et al., 2013) only quantitative evidence for the first effect can be found.
By comparing trajectories for different treatment choices, that is, with different quality of life weights per health state and costs, the direct effects of different treatment choices may be evaluated.	Treatment choices will impact on the quality of life and the costs of care (Andrews et al., 2004).
A 5-year time horizon is considered appropriate to capture the full effects in the scenarios and estimate the cost-effectiveness of the stepped-care and usual-care scenarios.	Since the treatment trajectories in the scenarios can take one year, and the time span of both the recovery probability curve and the relapse probability curve was two years, a time horizon of five years was chosen.

allowing every month a transition to another health state. Each health state is accompanied by quality of life weights and costs. Probabilities that depend on duration in a certain state guide the transitions from one health state into another. That is, the longer the length of an episode of MDD, the lower the probability to recover. Also, the longer patients are recovered, the lower the probability of having a relapse or recurrence. Textbox 1 lists the assumptions and their justifications that underpin the model.

2.7. Analyses

2.7.1. Health care perspective

All analyses were conducted from the health care system's perspective. Owing to a lack of quantitative evidence, we conservatively assumed that the guideline-congruent care has effects on recovery and risk of relapse similar to (and not better than) CAU (see Textbox 1).

2.7.2. QALYs

Quality adjusted life years (QALYs) are used in health research as a summary measure to evaluate overall health benefits of interventions. QALYs reflect the health state of a person in such a way that one QALY

stands for one year of life in perfect health. The standardization of health outcomes with QALYs enables decision makers to make comparisons across interventions, diseases or populations, and to decide on the willing to pay per QALY gained (Torrance & Feeny, 1989). The effectiveness of guideline-congruent care following the stepped-care algorithms was modelled through the transition probabilities from one health state to another in cycles of four weeks (0–4 weeks, 4–8 weeks, etc.). Quality of life scores (utilities) for the different health states enabled us to perform a cost-utility analysis with incremental costs per Quality Adjusted Life Year (QALY) gained. Utility scores on a scale of 0–1 associated with the different health states based on preferences, with a higher utility for more preferable health states, were multiplied with the duration of time spent in that health state to result in total QALYs. Estimates of utility scores for states of MDD were calculated as 1-(disability weight) based on disability weights for respectively mild MDD (0.19) and moderate or severe MDD (0.51) as found by Kruijshaar et al. (2005).

Effectiveness of the treatment interventions in the stepped-care scenarios were expressed as the standardized mean difference (i.e. Cohen's d and Hedge's g for small samples). The magnitude of Hedge's g and Cohen's d are interpreted using Cohen's convention as small (0.2), medium (0.5) and large (0.8) (Hedges & Olkin, 1985). These standardized mean differences were mapped onto the utility scores in the MDD states in order to calculate QALY-effects. For this, as in previous studies (Lokkerbol et al., 2014), we followed Vos et al. (2004), by which a health gain of $d = 0.5$ results in a corresponding health gain of 0.075 utility, using the conversion factor of 0.15 of Sanderson et al. (2004). Comparing total QALYs for each scenario results in QALYs gained.

2.7.3. Costs

Costs of care in each scenario were estimated by multiplying the units of health care consumption with the unit's standard integral costing price as recommended (Hakkaart-van Roijen et al., 2015; Oostenbrink et al., 2000). The unit costs per type of care, with 2007 as reference year, are listed in supplemental Table S1. The time horizon for estimating the costs and benefits of the stepped-care scenarios relative to the CAU-reference scenarios was five years. In accordance with the Dutch guideline for economic evaluations in health care, after the first year, costs were discounted at a constant rate of 4% per year and future effects at a constant rate of 1.5% per year (Zorginstituut Nederland, 2016). We indexed the costs to the year of 2017 as far as key outcomes are concerned by multiplying 2007 costs with a factor 1.166831113 based on the Dutch consumer price index obtained from Statistics Netherlands between 2007 and 2017 (http://statline.cbs.nl/Statweb).

2.7.4. Cost-effectiveness analysis

The incremental cost-effectiveness ratios (ICERs) express the cost-utility of the stepped-care algorithms as incremental cost per QALY gained.

For all scenarios we conducted probabilistic sensitivity analysis to assess the uncertainty around the incremental cost-effectiveness ratios and to ascertain the robustness of our results. The uncertainty ranges for the health care costs are described per scenario in Table 1 and in supplemental Tables S2 and S3. Uncertainty ranges for costs are the lower and higher bounds of estimations, with the peak estimations in the triangular distributions as the most likely value. The uncertainty ranges for the effectiveness of treatment interventions in the guideline-congruent care scenarios are given in supplemental Table S4. The distribution functions used in the probabilistic sensitivity analysis are also shown in supplemental Table S4. The probability curves for recovery and relapse used in the probabilistic sensitivity analysis, defined a priori, are reported in Van den Berg et al. (2011).

From the distributions of costs and effects in the depression state-transition model, parameter values for costs and effects were simulated in 5,000 runs. Probabilistic sensitivity analysis means specifying a joint

Table 1

Cost of care consumption in guideline-congruent care and care as usual for mild and moderate - severe major depressive disorder.

	Guideline-congruent care			Care as usual		
	Lower bound	Peak	Upper bound	Lower bound	Peak	Upper bound
Mild MDD	€ 254	€ 477	€ 693	€ 231	€ 401	€ 1049
Moderate –severe MDD	€ 906	€ 1113	€ 1736	€ 482	€ 850	€ 2019

Mental health care intervention costs in guideline-congruent care and care, for mild major depressive disorder (MDD) patients, and moderate-severe MDD patients. Peak (most likely) values with their lower and upper boundaries are given. Peak and boundary costs (in 2007 Euros) were estimated by an expert committee and modelled as a triangular distribution.

probability distribution to characterise uncertainty in the model's inputs and propagating that uncertainty through the model to derive probability distributions for its outputs (Doubilet et al., 1986). The usual way to propagate the uncertainty in a probabilititistic sensitivity analysis is Monte Carlo simulation, that is to run a sufficiently large number of simulations (e.g. the 5,000 we choose), each with a different set of parameter values obtained by drawing random from the distributions around each of the parameter estimates (in Table S4). The resulting cloud of cost-effectiveness outcomes reflect the spread of ICERs. This approach is preferred because the ratio nature of the ICER outcome and the relative complexity of the underlying simulation model implies that analytic derivation of the correct confidence interval is mostly intractable.'

Cost-effectiveness acceptability curves were created to show the probability that following the stepped-care algorithms in comparison to CAU is cost-effective as a function of the budget that policy makers are willing to pay for gaining an extra QALY. According to Dutch guidelines, willingness to pay (WTP) reference values vary with the disability weight of a disorder between €20,000 to €80,000 per QALY (Zwaap et al., 2015). For depressive disorder, with a mean disability weight of 0.46 (Kruijshaar et al., 2005), this implies a maximum WTP of €50,000 per QALY gained. A more conservative ceiling of €20,000 per QALY (for disability weights between 0.10–0.40) is also reported. The health-economic modelling and related analyses were performed with the R software for statistical computing.

3. Results

3.1. Two guideline-congruent stepped-care scenarios

3.1.1. Stepped-care for mild MDD, coverage rates and effectiveness

While 50% of the patients with a depressive episode will recover within three months, for the remaining patients the episode duration is on average 6 months (Spijker et al., 2002). The scenario for mild MDD describes the first half year after starting with treatment when 40% of the patients (expert estimate) typically receives the basic interventions (effect size as in CAU) or, in 60% of the patients, patients receive both basic interventions and minimal interventions including bibliotherapy or (online) self-management (effect size $\underline{d} = 0.84$, 95% CI 0.65–1.02) (den Boer et al., 2004).

For mild MDD, guideline-congruent care includes monthly contact with the general practitioner in step 1 and with both general practitioner and psychologist or psychotherapist in step 2, consisting of PST or BT (effect size $d = 0.83$, 95% CI 0.45–1.21; Cuijpers et al., 2007b). In step 3, for the 20% of the patients (expert estimate) with a mild episode of MDD that have not recovered in step 2, first psychotherapy, then either psychotherapy or pharmacotherapy is prescribed. Subsequently, for the patients that do not benefit from either psychotherapy or

antidepressants, combination therapy is indicated. For these patients, the care consumption can resemble CAU with a similar effect on quality of life and per-patient costs.

3.1.2. Stepped-care for moderate and severe MDD, coverage rates and effectiveness

For moderate and severe MDD treatment typically results in a remission of 76% (Spijker et al., 2002) while for the patients who will not be recovered, guideline-congruent care can resemble CAU. In the main scenario, guideline-congruent care includes contact with the general practitioner every two weeks and monthly antidepressant prescriptions during 8 months for 50% of the patients and for the other 50% contact with a psychotherapist (25%) or psychiatrist (25%) every two weeks (expert estimates). An effectiveness estimate for psychotherapy of $g = 0.531$ (95% CI 0.345–0.717) was applied in the model (Haby et al., 2006; de Maat et al., 2007).

3.2. Care-as-usual reference scenarios

3.2.1. CAU for mild MDD, coverage rates and mean value for quality of life

In the reference scenarios for mild episodes of MDD, 42% of the patients (expert estimate) receive pharmacotherapy. The other 58% of the patients (expert estimate) receives a mix of care. In this scenario, the lower bound of the cost estimate of care consumption is equal to the estimate in the NEMESIS study (Kruijshaar et al., 2005). For the higher bound of the costs of CAU we estimated contacts with both the general practitioner and the psychologist or psychotherapist to take place every two weeks and prescription of antidepressant medication for 70% of the patients. The estimate of the effect as utility score 0.81 (fixed) (Kruijshaar et al., 2005).

3.2.2. CAU for moderate and severe MDD, coverage rates and mean value for quality of life

In the reference scenario for moderate and severe episodes of MDD, the 25% of the patients not improving in 32 weeks receive inpatient care, day care and homecare. The estimate of the effect as utility score is 0.49 (fixed) (Kruijshaar et al., 2005).

3.3. Health care costs of stepped care and usual care

Cost estimates of health care consumption in the scenarios for guideline-congruent care and CAU in the main analysis (mean cost estimates) and in the uncertainty analyses with lower and higher bounds of corresponding health care costs, are described in Table 1.

In the stepped-care scenario for mild MDD, the lower bound of the estimated costs of care consumption was based on a contact frequency of once in six weeks over a period of 6 months with these caregivers and the lowest estimation of care consumption in individual studies as discussed in meta-analyses including minimal interventions (den Boer et al., 2004) and PST or BT (Cuijpers et al., 2007b). The higher bound of the estimate of the costs of care consumption in mild MDD was based on contact with the caregiver every two weeks and the highest estimate of

care consumption in individual studies as discussed in these meta-analyses.

For moderate and severe MDD in the stepped-care scenario, the lower bound of the cost estimate is based on a consult with the general practitioner every four weeks, six prescriptions of antidepressant medication in 50% of the patients and no differences with the main scenario in contact with the psychologist, psychotherapist or psychiatrist. The higher bound of the cost estimate is based on weekly contacts with the general practitioner and eight prescriptions of antidepressant medication for 50% of the patients and monthly contact with the psychologist or psychotherapist in 50% of the patients and with the psychiatrist in 25% of the patients.

In the reference scenario for mild MDD, the lower bound of the cost estimate of care consumption is equal to care consumption in the NEMESIS study (Kruijshaar et al., 2005). For the higher bound of the costs of CAU we estimated contacts with both the general practitioner and the psychologist or psychotherapist to take place every two weeks and prescription of antidepressant medication for 70% of the patients.

In the reference scenario for moderate and severe episodes of MDD, cost estimates were obtained including and excluding care that is used by the 25% of the patients (expert estimate) not improving in 32 weeks (i.e. inpatient care, day care and homecare). This resulted in an estimate of the lower and higher bounds and the average costs of care for moderate and severe MDD.

Detailed descriptions of the coverage rates, type and amount of care consumption and corresponding costs in the guideline-congruent and CAU scenarios, with lower and higher bounds of the estimates in the main scenarios as used in the sensitivity analyses, are available as supplemental Tables S2 and S3.

3.4. Incremental effects

The incremental effects consist of the assumed effects on quality of life through treatment in the stepped-care scenarios compared to CAU-reference scenarios. Resource use and accompanying effects on quality of life that are assumed the same in the stepped-care and usual-care scenarios are ignored. The difference in treatment effects over the 5 year time horizon resulting from the simulations is a gain of 0.014492 QALY in mild MDD and 0.014831 QALY in moderate and severe MDD, implying modest but significant health gains (see Table 2 and Fig. 4).

3.5. Cost-utility analysis

The cost-utility analysis comparing differential treatment effects of the stepped-care algorithm for mild episodes of MDD versus CAU showed better health outcomes and less costs in favour of guideline-congruent stepped care, implying dominance of the guideline-congruent care. The cost-utility analysis comparing differential treatment effects of the stepped-care algorithm for moderate and severe MDD versus CAU suggested better health outcomes following the guideline-congruent stepped-care algorithm against more costs, with a mean ICER of €2,700 (about €3,200 in 2017 euro) per QALY gained. The

Table 2
Incremental costs, incremental effects and mean ICER for mild and moderate - severe major depressive disorder.

Depression severity	Incremental costs	Incremental Effects (QALYs)	Mean ICER	ICERs in NE quadrant (%)	ICERs in SE quadrant (%)	ICERs in NW quadrant (%)	ICERs in SW quadrant (%)
Mild MDD	€ −36.72	0.014492	€ −2534	2.64	67.36	0	0
Moderate - severe MDD	€ 46.96	0.014831	€ 3166	67.16	32.84	0	0

Incremental costs, incremental effects (in Quality Adjusted Life Years - QALYs) and mean incremental cost-effectiveness ratios (ICERs) for mild major depressive disorder (MDD) and moderate-severe MDD.
NE = North East, SE = South East, NW = North West, SW = South West. Costs are indexed to 2017 Euros. As can be observed from this table, guideline-congruent care leads to a negative mean ICER compared to care as usual, i.e. a relative gain in QALYs at lower costs. Hence, guideline-congruent care dominates care as usual in case of mild MDD. For moderate-severe MDD, a relative gain in QALYs with guideline-congruent care is achieved at somewhat higher costs.
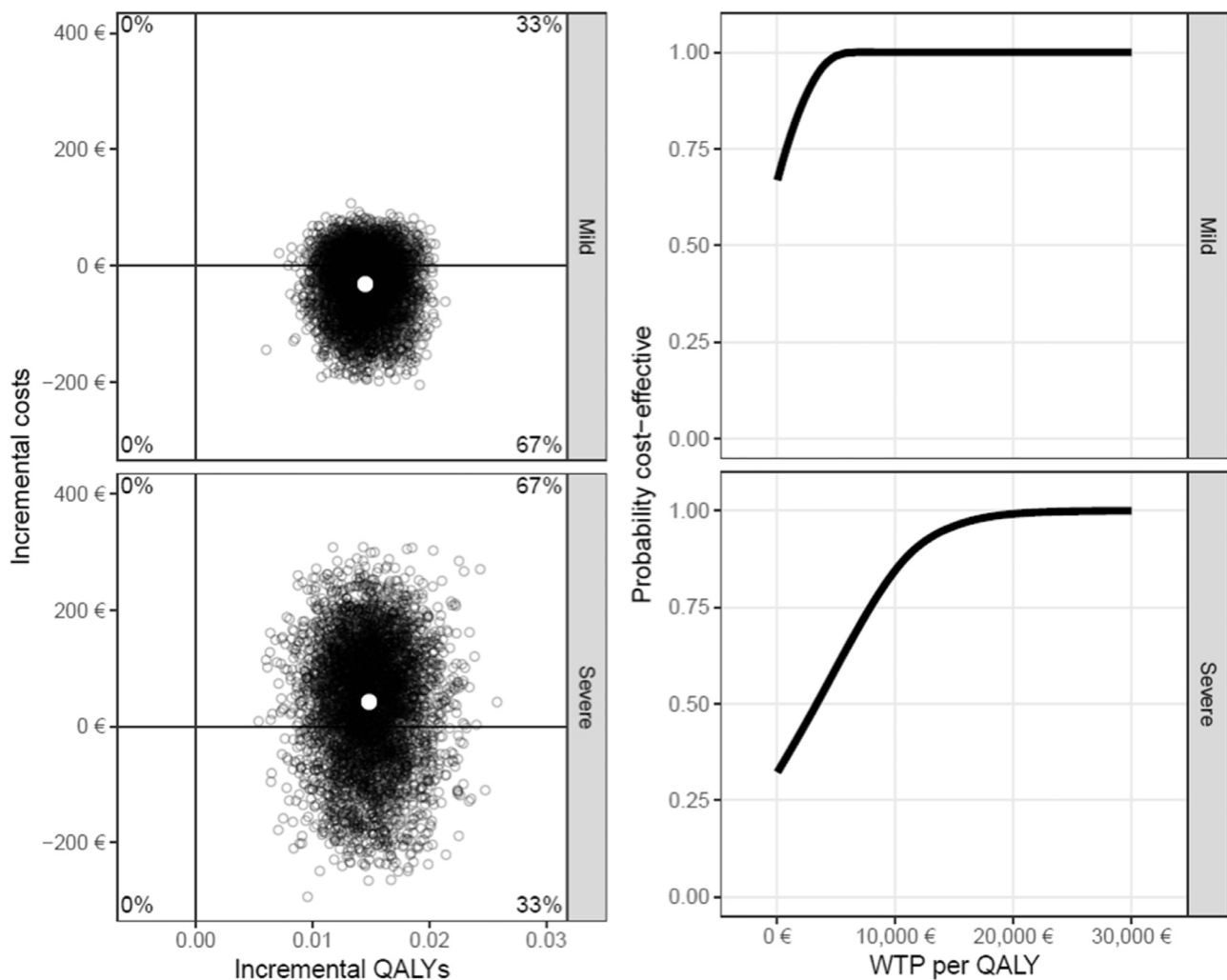
Fig. 4. Cost-effectiveness planes and acceptability curves for stepped-care versus care as usual for mild major depressive disorder (MDD) and for moderate and severe MDD.

Left panel: Cost effectiveness planes with incremental effects in QALYs (on the x-axis) and incremental costs in € (on the y-axis) in the stepped-care scenarios versus care as usual for mild MDD (upper left) and moderate and severe MDD (lower left). Right panel: Cost-effectiveness acceptability curves showing the chance (P) that applying the stepped-care algorithm is cost-effective (on the y-axis) in € per QALY, for various willingness to pay (WTP) ceilings (on the x-axis) for mild MDD (upper right) and for moderate and severe MDD (lower right).

incremental costs and effects and the Incremental Cost-Effectiveness Ratio (ICER) for the stepped-care scenarios are summarised in Table 2.

Results of the 5,000 simulated ICERs are presented in the cost-effectiveness planes in Fig. 4 (left panel) with on the x-axis incremental utility (health gains in QALYs) and on the y-axis the incremental costs, both per person per year. The northeast quadrant displays health gains at additional costs and the southeast quadrant displays health gains accompanied by cost reductions. In all scenarios, 100% of the simulated ICERs fall into the right side of the y-axis, reflecting health gains. The results show that in terms of the incremental costs per QALY, the stepped-care algorithms for both mild MDD and moderate or severe MDD are associated with greater health gains as compared to CAU.

For mild episodes of MDD, in 33% these health gains come with additional costs, while 67% of the simulated ICERs fall below the x-axis reflecting cost reductions, which suggests that there is a likelihood of 67% that stepped-care is associated with better health outcomes and lower costs, compared to CAU. The stepped-care approach is then deemed to be 'dominant' (i.e. to dominate CAU in terms of cost-effectiveness). For moderate and severe episodes of MDD, in 67% health gains come with additional costs, and stepped care is less expensive than CAU in 33% of the simulated ICERs.

The cost-effectiveness acceptability curves in the right panel in

Fig. 4 show that when applying a relatively modest WTP threshold of €10.000 per QALY, the probability that the stepped-care algorithm for mild episodes of MDD is cost-effective is above 95%. For moderate and severe episodes of MDD, the cost-effectiveness acceptability curve shows a 80% probability that stepped care is cost-effective for a WTP threshold of €10.000 per QALY. When applying an acceptable threshold of €20.000 per QALY, both stepped-care algorithms have a probability above 95% of being cost-effective compared to CAU.

4. Discussion

4.1. Main findings

This modelling study shows that health gains can be achieved cost-effectively following stepped-care algorithms according to clinical guideline recommendations. The model simulations suggest that stepped care compared to usual care for mild MDD results in better health outcomes against lower costs in favour of guideline-congruent stepped care (dominant). For moderate and severe MDD, one extra QALY is gained at relatively low costs of on average about €3,200 (in 2017 euros) for guideline-congruent care compared to CAU. The sensitivity analyses show that the results are robust. This implies that it is

highly likely that stepped care is a cost-effective choice compared to CAU at acceptable willingness-to-pay (WTP) levels per QALY gained.

Our hypothesis, that in stepped care health gains can be achieved cost-effectively, was confirmed. The results from our cost-effectiveness analyses were not only due to differences in costs. The sensitivity analyses supported the robustness of the additional health benefits of the stepped-care scenarios; these were small, but positive in all sensitivity analyses. Apparently, for moderate or severe MDD, stepped care resulted in more intensive treatment regimens, i.e. higher costs, but also yielded clinically relevant effects over and beyond usual care.

Our depression state-transition model analyses are in line with previous findings in other cost-effectiveness studies evaluating depression guideline recommendations. The Improving Access to Psychological Therapies (IAPT) stepped-care approach based on the NICE guideline was associated with small gains in QALY and resulted in an ICER of £29,500 per QALY (Mukuria et al., 2013). Although surrounded with uncertainty around the costs and outcome, the IAPT service was within the NICE threshold of £30,000 per QALY. A modelling study in the UK comparing pharmacotherapy with cognitive-behavioral therapy (CBT) and combination treatment for moderate and severe depression in secondary care found that CBT as monotherapy was most likely to be the most cost-effective treatment option above a threshold of £22,000 per QALY with an incremental cost-effectiveness ratio of £20,039 per QALY compared with pharmacotherapy (Koeser et al., 2015).

4.2. Limitations of this study

Any modelling study depends on the accuracy of input parameters and model assumptions. Although we made all assumptions conservatively, there are several limitations we should mention.

First, the depression state-transition model is based on the Australian model of Vos et al. (2005), which was adapted for the Dutch situation. The current model and its outcomes can therefore not be generalised to health care systems in other countries without knowing that in usual care in the Netherlands all patients have universal health insurance coverage and fair access to a range of treatments for depressive disorder.

Second, the number of studies on effect sizes specified for the severity of the depressive disorder (mild versus moderate and severe MDD) was restricted. We based the estimations of the effect sizes on a limited number of treatment outcome studies. Therefore, we applied probabilistic sensitivity analyses with conservative uncertainty ranges around the effect sizes.

A patient's future relapse and recurrence rate increases with the number as well as the duration of depressive episodes while treatment interventions differ in effect on the probability of recovery or relapse (Bockting et al., 2015; Beshai et al. 2011). However, evidence about how duration of the depressive episode or the number of recurrent episodes relates to treatment effects, is lacking. Therefore, we did not model the disease history regarding the number of depressive episodes, but we did model the effect of duration of depressive episodes on recovery and relapse. The model conservatively assumed that stepped-care strategies and usual care have similar recovery and relapse rates. The modelled scenarios are an underestimation of the true effects when the guideline recommendations do not only impact on quality of life but also improve recovery and/or reduce relapse rates, for example, through better adherence by caregivers, better compliance by patients to their treatments or lower drop-out rates.

Furthermore, according to the Dutch multidisciplinary guideline, observed partial recovery is informing clinical decisions on continuing treatment or stepping up to then more appropriate treatment. Also, it is known that the pathway to complete recovery runs via partial recovery (Spijker et al., 2002; Bockting et al., 2006). Currently available data do not allow modelling the transition rate from mild MDD to moderate or severe MDD. Although conceptually desirable, the present model makes no distinction between partial and complete recovery and in that sense is not reflecting guideline-congruent care, which is a limitation. However, an augmented number of health states in the depression-state transition model would introduce uncertainty while evidence on the costs and effects distinguishing partial and complete recovery is still limited.

We restricted the costs to direct health care costs, which limits our findings. When different effects on productivity between guideline-congruent care and usual care were assumed, the impact on our results would be limited. However, not including the indirect costs may lead to underestimation of the wider costs of depression (Mohseninejad et al., 2013; Andrews et al., 2004). In case the step-up treatment would in line with clinical results be accompanied by improved participation, the cost-effectiveness would obviously have turned out more favourable.

Costs for monitoring and treatment evaluation, needed for timely stepping up to subsequent interventions were included in the contact with the caregiver. Implementation costs, such as for costs needed to deliver interventions without waiting lists as part of an integrated care model, programme management and administration, training and supervision, strengthened logistics and information systems (Chisholm et al., 2016), were not included in the cost calculations. On the other hand, all assumptions in our modelling study were made conservative, resulting in cautious estimates of the possible effects of following guideline recommendations.

It is questionable whether the basic interventions, consisting of 1. psychoeducation, 2. active monitoring, 3. structuring of the day, are current care as usual or not. In our study we assumed that they are not. If these basic interventions could be considered as usual care, the costs of usual care would increase, indicating that our analyses were conservative.

The stepped-care scenarios describe appropriate and acceptable care according to current guideline recommendations. These scenarios represent an ideal model of care and at the same time an abstraction of real care in which it is not possible to take account of all relevant individual differences. Therefore, these depression state-transition model analyses need to be considered as indicative, giving the picture for the average patient.

4.3. Implications for clinical practice

This study lends support to the idea that guideline-congruent care is likely to be more cost-effective than usual care. Hence, wider implementation of guideline-congruent care and facilitating caregivers to follow guideline recommendations may be encouraged. From studies on implementing these guidelines we know that treatment processes can be improved, but also that guideline implementation is complex (Hermens et al., 2014; van Dijk et al., 2013; Richards et al., 2012; Franx et al., 2009; 2014). In clinical practice, treatment decisions made by shared decision making, for example on the choice between psychotherapy or pharmacotherapy in severely depressed patients, can be informed by the stepped-care algorithms. To recognize patients who will not benefit from a lower-intensity intervention or for whom treatment delay could cause harm, close monitoring and evaluation of expected and observed treatment response is required.

The stepped-care algorithms account for depression severity, depending on the nature and number of symptoms, while allowing for stepping in based on patient preference, treatment history or other patient variables. Better treatment outcomes are expected when care is more personalised to the patient's needs. However, it is currently unclear which patient variables can be matched to treatment to establish desired patient outcomes, such as the number of depressive episodes. Future research is needed to adjust the stepped-care algorithms accounting for this heterogeneity.

This study revealed that stepped-care algorithms can be used as cost-effective decision support tools for clinical decision-making adjusted to patient's needs. The algorithms for mild episodes of major

depressive disorder will reduce over-treatment and inappropriate use of antidepressants, while the algorithms for moderate and severe major depressive disorder aim to offer adequate treatment as soon as possible while reducing under-treatment.

5. Conclusions

Based on our study we may conclude that adhering to the stepped-care algorithms is associated with health improvement. It is very likely that the stepped-care algorithms following the depression guideline recommendations are cost-effective relative to usual care for depression. The extra costs per QALY of the stepped-care algorithm for mild episodes of MDD are with more than 95% certainty lower than €10,000. The extra costs per QALY of the stepped-care algorithm for moderate and severe MDD are with more than 80% chance lower than €10,000 and with more than 95% chance lower than €20,000. This implies that guideline-congruent care is acceptable from a cost-effectiveness perspective. Our findings supports clinical decision-making guided by stepped-care algorithms that are congruent with current guideline recommendations.

Declarations of interest

None.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.08.024.

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