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ECONOMIC EVALUATION

Cost-Effectiveness Analysis for Antidepressants and Cognitive Behavioral Therapy for Major Depression in Thailand

Benjamas Prukkanone, MD^{1,*}, Theo Vos, MD, PhD², Melanie Bertram, PhD², Stephen Lim, PhD³

¹Department of Mental Health, Galaya Rajanagarindra Institute, Ministry of Public Health, Bangkok, Thailand; ²Center of Burden of Disease and Cost-Effectiveness, School of Population Health, University of Queensland, Brisbane, Australia; ³Institute for Health Metrics and Evaluation, School of Public Health, University of Washington, Seattle, WA, USA

A B S T R A C T

Objective: To determine the cost-effectiveness of fluoxetine and cognitive-behavioral therapy (CBT) for major depression in Thailand. **Methods:** A microsimulation model was developed to describe the variation in course of disease between individuals. Model inputs included Thai data on disease parameters and costs while impact measures were derived from a systematic review and meta-analysis of the international literature. Fluoxetine as the cheapest antidepressant drug in Thailand was analyzed for treatment of episodes plus a 6-month continuation phase and for maintenance treatment over 5 years of follow-up. CBT was analyzed for episodic treatment and for 5-year maintenance treatment. Results are presented as cost (Thai bahts) per disability-adjusted life-year (DALY) averted, compared with a “do-nothing” scenario. **Results:** The cost-effectiveness ratios of all interventions were below 1 time Thailand’s gross domestic product of 110,000 bahts per capita. The uncertainty ranges

around the cost-effectiveness ratios overlap: maintenance treatment with CBT 11,000 bahts per DALY (8,000–14,000); episodic treatment with CBT 23,000 bahts per DALY (10,000–36,000); episodic plus continuation drug treatment 33,000 bahts per DALY (26,000–44,000); maintenance drug treatment 38,000 bahts per DALY (30,000–48,000); and episodic drug treatment 42,000 bahts per DALY (32,000–57,000). **Conclusions:** CBT and generic fluoxetine are cost-effective treatment options for both episodic and maintenance treatment of major depression in Thailand. Maintenance treatment has the greatest potential of health gain.

Keywords: health economics, major depressive disorder, pharmacotherapy, psychotherapy.

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Introduction

Major depression has a large health and economic impact on individuals and communities. Up to 15% of patients with depression die from suicide over their lifetime [1]. By the year 2020, if the current demographic trends and epidemiological transition continue, the burden of depression will increase to 5.7% of the global burden of disease, becoming the second leading cause of disability-adjusted life-years (DALYs) lost, eclipsed only by ischemic heart disease in both males and females [2]. According to the Thai Mental Health Survey 2003, major depression was the most prevalent mental disorder in Thailand (3.2%; 95% confidence interval [CI] 2.9–3.5) [3]. Depressive disorder also imposes a significant burden in Thailand. It ranked as one of the top 10 causes of DALYs lost in Thailand in 1999, coming first for females and fourth for males [4]. Depression is also a costly disease. The high costs are not only the direct treatment costs, but there is also a large contribution from indirect costs including absenteeism, loss of opportunity, and productivity [5].

Previous studies have found that there are a variety of treatment options for improving the quality of life and social function of patients who have major depression [6–8]. In addition, effective treatment can decrease the financial burden of illness by reducing the direct and indirect costs associated with depression [9]. Effective interventions include antidepressant drugs and various methods of psychotherapy. The first-line treatment for most people with depression today consists of antidepressant drug therapy, psychological interventions, or a combination of the two. Among the psychotherapeutic approaches, cognitive-behavioral therapy (CBT) is an intervention recommended by clinical practice guidelines for the treatment of depression [7,8]. In Thailand, these interventions are currently recommended by the clinical practice guidelines for the treatment of major depressive disorder of the Royal College of Psychiatry of Thailand and the Psychiatric Association of Thailand [10]. CBT, however, is currently only sporadically available in Thailand. In general, the country has very few people with any psychotherapeutic skills. There are a number of antidepressant drugs in Thailand. Only two of them have generic versions available, fluoxetine and sertraline.

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* Address correspondence to: Benjamas Prukkanone, 23 Galaya Rajanagarindra Institute, 4th Phutthamonton Road, Tawewattana, Bangkok 10170, Thailand.

E-mail: benjamas.prukkanone@uqconnect.edu.au.

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Despite there being a range of options for treating patients with depressive disorders, even in high-income countries only one-third of patients receive effective treatments [11,12]. Even recently, the health insurance schemes that covered all Thai people—6 million (9%) covered by the Civil Servant Medical Benefit Scheme, 10 million (16%) covered by the Social Health Insurance scheme, and the rest of the population (47 million) covered by the Universal Coverage scheme [13]—estimated that only 4% of psychiatric patients received treatment [14]. In Thailand, resources currently allocated to meet the needs of patients with mental disorder are scarce [15]. Given finite resources in mental health personnel and budget, economic evaluation can help to determine the most cost-effective interventions among numerous intervention options available. Such evidence can help policy decision makers set priorities in terms of budget allocation [16].

Two articles have reviewed the effectiveness of CBT by newly trained Thai CBT therapists in Thai depressive patients [17,18]. Both were outcomes of a project to train mental health professionals in the treatment of major depression by CBT. In the first phase, 10 experienced mental health professionals were trained in a 5-day workshop by a qualified trainer from the United Kingdom. All trainees received at least eight sessions of supervision from two qualified Thai therapists. During the training, a Thai manual of CBT for depression was developed. In the last phase of the project, a 16-week, open-label study of the efficacy and acceptability of CBT in patients with major depression not responding to 4-weeks of treatment with fluoxetine was carried out.

The first study [18] reported outcomes in 15 patients treated by four newly trained therapists. Overall, the treatment program seemed effective in alleviating depression (13 of the 15 patients improved significantly), and patient satisfaction with treatment was high. Fifty-seven percent of patients, however, stopped treatment before week 12; only one completed all the 16 sessions. The authors concluded that CBT efficacy as evident in Western studies can be generalized to the Thai context. Nevertheless, the high discontinuation rate suggests that patients may prefer a shorter duration of treatment. The other study [17] reported that all 10 patients, of three newly trained therapists from this same CBT training program, responded by week 12 and 70% of them were in remission by week 12. Neither study had a control group and therefore provide insufficient evidence of effectiveness.

There is only one cost-effectiveness study of drug treatment of major depressive disorder in Thailand. It concluded that escitalopram was more cost-effective than fluoxetine and venlafaxine, but it did not consider the availability of a cheap generic version of fluoxetine [19]. There are no economic evaluations of psychotherapy in Thailand. Our study aims to inform policymakers of the most cost-effective intervention for major depression in Thailand.

Methods

Cost-effectiveness analysis is a method of assessing the health consequences relative to the costs of different health interventions. It is used to identify health interventions that yield the highest benefit in health outcomes per monetary unit of health expenditure [20].

Framing and design of the analysis

This study adopted a “health sector” perspective, arguing that it is most suitable to policymakers as part of decision making in health resource allocation. This perspective concerns the health-related costs borne by government and by individuals including time and travel costs. The comparator was a hypothetical “do-nothing” scenario-based on the generalized Cost-Effectiveness Analysis framework [21]. The target population in this study was those in

the Thai population in 2005 experiencing a major depressive episode. The time horizon for evaluating the benefits and costs of interventions for depression was over a 5-year follow-up period. This time horizon was considered appropriate for tracking the costs/cost offsets and consequences associated with the selected interventions as there was no information on the longer-term consequences of these interventions beyond 5 years. In addition, the natural history of depression can be reasonably described over a 5-year period, but there is a lack of data to accurately describe the course of major depression over a lifetime.

A 3% discount rate that matches the rate chosen in the Thai burden of disease study [4] was applied to both costs and benefits. It is also the rate of discounting recommended by a consensus panel of health economists in the United States [22], and it was in the range of 3% to 5% recommended by economic evaluation guidelines in Thailand [23].

Description of interventions

Pharmacological interventions and CBT were selected for analysis by the steering committee and the expert advisory group for mental health in the Setting Priorities using Information on Cost-Effectiveness (SPICE) project, which was a collaborative project between the Ministry of Public Health, Thailand, and the University of Queensland, Australia. We undertook the current study as part of the SPICE project, which aimed to address key information gaps on burden of disease and cost-effectiveness across multiple disease areas in Thailand, with regard to policy concerns and technical rationality. The SPICE project included a cause of death study that aimed to improve the quality of cause of death statistics by deriving a “best” estimate of true cause-specific mortality in Thailand based on verbal autopsy interviews of 11,000 deaths and review of available medical records [24–27].

The interventions were classified by three phases of treatment: First, the acute or episodic phase is the time period from the initiation of treatment to remission (i.e., decrease in depressive symptoms to “normal”), which usually lasts between 8 and 12 weeks [12]. Second, the continuation phase is the period following the episodic phase for preventing relapse (i.e., the return to major depression). At least 6-months continuation therapy has been recommended by guidelines for the treatment of major depressive disorder [8,28]. Third, maintenance treatment may be given during a 5-year period following an episode to prevent recurrence (i.e., a new episode of major depression following recovery).

The drug interventions for major depression include the older tricyclic antidepressants, amitriptyline; the newer serotonin reuptake inhibitors, fluoxetine, sertraline, and escitalopram; and the newer serotonin norepinephrine reuptake inhibitor, venlafaxine. Generic serotonin reuptake inhibitors cost less than 10% of the cost of patented medications in Thailand. Meta-analyses show no difference in efficacy between antidepressant drugs [29,30]. Therefore, we analyzed generic fluoxetine only as the lowest cost antidepressant and the most commonly prescribed serotonin reuptake inhibitor in Thailand [31].

CBT is a nonpharmacological intervention that is effective in the treatment of depression alone or combined with drug therapy. A course of CBT during or following an acute episode has been found to prevent relapse for up to 1.5 years after an episode [32] and to further reduce recurrence if booster sessions are given as maintenance treatment [33,34]. CBT is a highly structured approach to psychotherapy with a shorter duration than most other therapies. The assumption of CBT is that emotional and behavioral problems are caused by cognitive or thought dysfunction. CBT is based on collaborative work between the therapist and the client. The therapist helps the client to identify emotions or feelings, negative automatic thoughts, and schema or core beliefs. This leads to modification of automatic thoughts and core beliefs in the end [35].

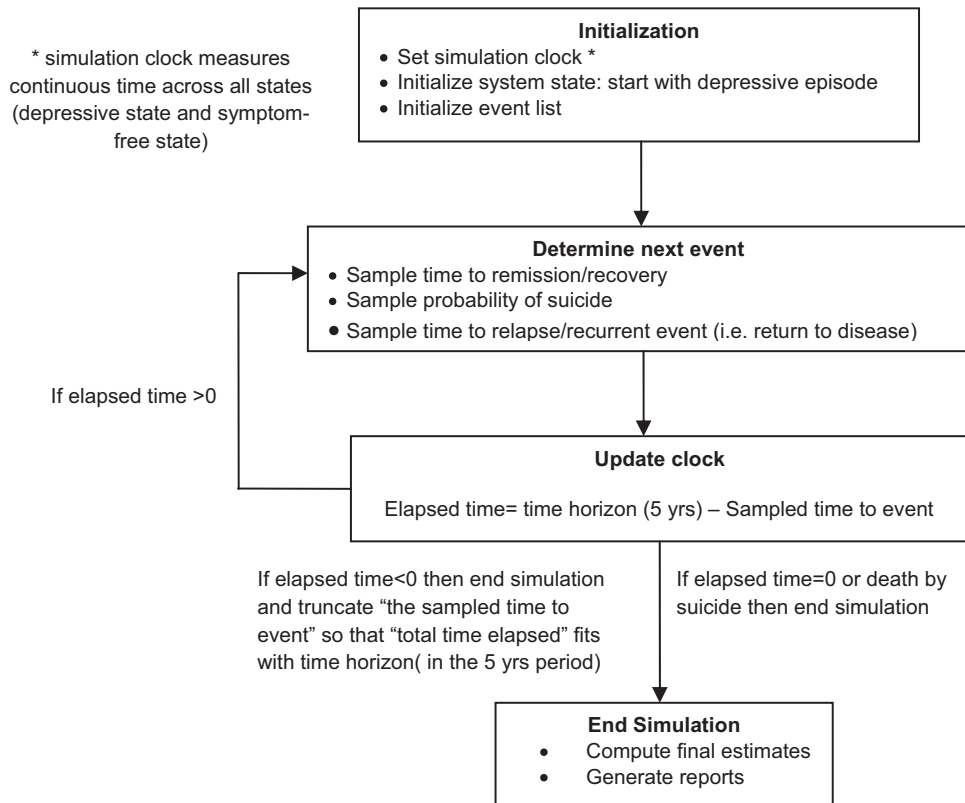


Fig. 1 – Graphical representation of the algorithm of discrete event simulation model (adapted from Le Lay et al. [38] and Caro [39]).

Modeling

The disease model has a mathematical structure that represents the health outcomes of 8000 hypothetical patients under five scenarios: episodic drug treatment, continuation drug treatment, maintenance drug treatment, episodic CBT treatment, and maintenance CBT treatment. We chose this hypothetical number because it was enough to get a stable model that reflects the variability in the course of the disorder. As major depression is a recurrent disorder with large variations in duration of episodes and time to the next episode, a discrete event simulation model was chosen to evaluate the costs and consequences of interventions for major depression.

The model structure was based on the model developed for the Assessing Cost Effectiveness of Mental Health (ACE-MH) study in

Australia [36]. The ACE-MH model only derived an average number of episodes and proportion of follow-up time with depression from microsimulation and applied these averages as inputs to a deterministic cost-effectiveness model. This study uses simulation modeling of individual-level data all the way through to the determination of costs and benefits.

This model was constructed in Microsoft Excel by using the add-in Ersatz software for uncertainty analysis [37]. Each individual patient was simulated over a 5-year period through the natural history of depression (age, sex, and suicide risk). The model used continuous time; thus, it was not restricted by a fixed cycle length. Time to next event was determined stochastically from a specified distribution. Each individual could have periods of depression and episode-free periods of varying lengths. The algorithm of this discrete event simulation model as shown in Figure 1 was adapted from Lay et al. [38] and Caro [39].

Table 1 – Effectiveness parameter values and sources of information.

| Parameter | Value (95% confidence interval) |
|---|---------------------------------|
| RR suicide on treated vs. untreated depression | 1.80 (1.60–2.00) [37] |
| Effect size of antidepressant drugs | 0.32 (0.25–0.40) [39] |
| Effect size of CBT | 0.77 (0.44–1.10) [11] |
| RR relapse during 6-mo continuation of drug treatment | 0.42 (0.32–0.56) [11] |
| RR relapse in 18 mo following CBT | 0.64 (0.51–0.78) [11] |
| RR relapse for drug/CBT maintenance treatment | 0.44 (0.39–0.49) [11] |

CBT, cognitive-behavioral therapy; RR, relative risk.

Table 2 – Cost input parameter values and sources of information.

| Parameter | Value (THB) (uncertainty range) |
|---|---------------------------------|
| Psychiatric outpatient operating cost per visit | 529 (436–585) [45] |
| Drug (fluoxetine) cost per day | 2 (1–3) [46] |
| Time cost per visit | 37 (46–28) [48] |
| Travel cost per visit | 24 (29–18) [49] |

THB, Thai baht.

Table 3 – Values and assumptions of number of visits for interventions.

| Intervention | Number of visits per year (uncertainty range) | Source |
|-----------------------------|---|----------------|
| Episodic drug treatment | 10 (8–12) | Expert advice* |
| Continuation drug treatment | 7 (6–8) | Expert advice* |
| Maintenance drug treatment | 5 (4–6) | Expert advice* |
| Episodic CBT treatment | 10 (8–12) | Expert advice* |
| Maintenance CBT treatment | 5 (4–6) | Expert advice* |

CBT, cognitive-behavioral therapy.
* From the expert advisory team for mental health in the Setting Priorities using Information on Cost-Effectiveness project.

Epidemiological data

We used data for the prevalence of major depression by age and sex from the National Mental Health Survey in 2003 [3] and used a lognormal distribution of data from international follow-up studies to mathematically describe the variation in length of episodes (μ 2.05, σ 1.60) and time between episodes (μ 2.35, σ 3.88) (12). In addition, we assumed a minimum of 2-week duration of an episode as stipulated by the *International Statistical Classification of Diseases, 10th Revision*, and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnostic criteria and applied a rule of a minimum of 8 weeks free of depression before it can be called a new episode of depression rather than a relapse back into the same episode [40].

During a depressive episode, patients are at increased risk of suicide. We used the relative risks of suicide with depression of 15.7 (95% CI 11.9–20.3) for males and 27.8 (95% CI 21.8–34.8) for females from a meta-analysis [41]. These relative risks along with the prevalence of major depression in Thailand were applied to the total number of suicide deaths from the SPICE cause of death study to calculate suicide deaths attributable to depression by age and sex. As part of fatal health consequences, we applied a relative risk of suicide for those on treatment versus those not on antidepressant treatment [42] to the number of suicide deaths attributable to depression by age and sex to determine a yearly suicide risk in those with treated and untreated depression.

Estimating intervention effectiveness

The measure of health gain chosen was the DALY. Health gain from the averted number of suicide deaths was estimated by multiplying

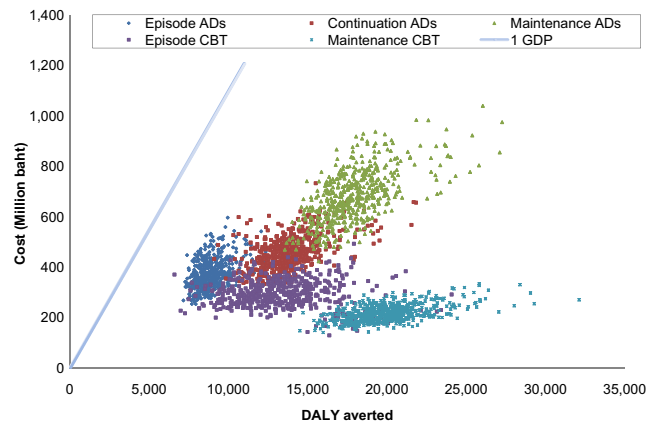


Fig. 2 – Cost-effectiveness plane for depression interventions. AD, antidepressant; CBT, cognitive-behavioral therapy; DALY, disability-adjusted life-year; GDP, gross domestic product.

each death with the remaining discounted health-adjusted life expectancy based on the life table generated for Thailand in 2005 from the SPICE cause of death study and the rates of prevalent years lived with disability from the 1999 Thai Burden of Disease study [4]. This rate of prevalent years lived with disability was taken as a proxy for the probability of nonfatal health loss by age and sex in 2005.

Nonfatal health outcomes were calculated in a number of steps. First, we translated pooled effect sizes (ESs) for each intervention from various trials into a change in the disability weight (DW) [43]. Because a number of scales are used for measuring mental health outcomes in trials, the ES of interventions was pooled as a standardized mean difference [44]. We used the ES of the antidepressant drugs from the Kirsch et al. [45] meta-analysis of data submitted to the Food and Drug Administration of the United States, which avoided the publication bias affecting other meta-analyses. We adopted an estimate of the average change in DW per ES calculated in the Australian ACE-MH study [46]. This was based on a DW of untreated depression (0.35) and a conversion factor of 0.16 (95% CI 0.14–0.17) per unit of ES adopted from the study of Sanderson et al. [47].

In addition to reducing disability during a depressive episode, drug interventions lower the risk of relapse if given as continuation and maintenance therapy. These data and the ESs for CBT came from meta-analyses conducted for the ACE-MH study [12] based on a previously published meta-analysis by Geddes and colleagues [48]. The effectiveness measures are summarized in Table 1.

Health benefits of interventions were ignored in patients not adhering to drug therapy or CBT. Adherence across all antidepressant

Table 4 – Total costs, DALYs averted, and cost-effectiveness ratios of depression interventions per 100,000 individuals with depression.

| Intervention | Total costs (million bahts) (95% uncertainty interval) | DALYs (95% uncertainty interval) | Cost-effectiveness ratio (95% uncertainty interval) |
|-----------------------------|--|----------------------------------|---|
| Episodic drug treatment | 370 (280–520) | 9,000 (8,000–11,000) | 42,000 (32,000–57,000) |
| Continuation drug treatment | 460 (350–600) | 14,000 (11,000–19,000) | 33,000 (26,000–44,000) |
| Maintenance drug treatment | 680 (500–900) | 18,000 (15,000–24,000) | 38,000 (30,000–48,000) |
| Episodic CBT treatment | 290 (180–410) | 13,000 (9,000–20,000) | 23,000 (10,000–36,000) |
| Maintenance CBT treatment | 210 (1,600–300) | 20,000 (16,000–26,000) | 11,000 (8,000–14,000) |

Note: All estimates rounded to two significant digits.
CBT, cognitive-behavioral therapy.

sants of 41% (95% CI 37%–46%) came from our own study, which evaluated an electronic prescription database of depressive patients in a psychiatric hospital in Thailand [31]. In the absence of data, we assumed the same adherence for CBT. The model also took into account a lag before patients seek treatment. Expert opinion sought for the ACE-MH study suggested that the lag period for treatment of depression is 2 to 4 weeks, and Thai experts agreed with this estimate.

Estimating intervention costs

Operating costs of an outpatient unit were derived from a study of the Department of Mental Health in 2000 [49]. The cost of drugs was estimated from the drug price list of the Medical Information Center, Department of Health Service Support, Ministry of Public Health in 2005 [50]. We used the consumer price index [51] to adjust costs in other years to those in 2005. The cost of CBT was calculated from the number of visits multiplied with the unit cost per visit for outpatients. Time cost was assumed to be 25% [52] of personal income per capita in Thailand in 2005 [53], and travel cost was calculated from the average cost of the return trip to the hospital by public transport from a Thai study [54]. Details of all costs are described in Table 2. The assumptions of numbers of visits per year for drug treatment and CBT are described in Table 3.

Cost-offsets (the reduction in hospital costs as a direct result of psychiatric treatment) were not included. Although there is evidence to support cost-offsets in other areas of psychiatric care, information of cost-offsets related to depression treatment is less clear [55–58].

Sensitivity and uncertainty parameters

The uncertainty in this study includes first-order and second-order uncertainty. First-order uncertainty analysis simulated the course of disease in a hypothetical cohort of 8000 individuals. The second-order analysis involved a multivariate probabilistic Monte Carlo simulation of 1000 iterations of the model to quantify the distribution in the cost-effectiveness ratios propagated from the uncertainty in the input data as listed in Tables 1 to 3. Uncertainty analyses were carried out in Excel with the Ersatz software add-in program (www.epigear.com).

Results

The results are presented as cost-effectiveness ratio in Thai bahts per DALY averted (Table 4).

Maintenance CBT had the lowest cost and averted the largest number of DALYs. Maintenance treatment with drugs cost three times more than CBT maintenance treatment. There was considerable overlap in uncertainty between the cost-effectiveness ratios (Table 4 and Fig. 2).

Discussion

The average cost-effectiveness ratios of all interventions were below 1 time the GDP of 110,000 bahts per capita in Thailand, a level recommended as a cutoff for “very cost effective” interventions [59].

CBT and generic fluoxetine are cost-effective treatment options for both episodic and maintenance treatment of major depression in Thailand. Maintenance treatment has the greatest potential of health gain.

As the large majority of depressive patients have multiple episodes over their lifetime, there are strong recommendations to treat major depressive disorder as a chronic episodic disease [8,28]. Hence, most people with major depression should receive longer-term medication treatment or psychotherapy during what

are called “continuation” or “maintenance” periods to prevent relapse and recurrence of the disorder.

CBT is currently only sporadically available in Thailand. CBT is not part of psychology or psychiatry training programs. There also is a lack of mental health personnel, especially psychiatrists and psychologists, who would be expected to deliver CBT in Thailand. It may be more feasible and would be less costly to train psychiatric nurses as CBT therapists rather than psychiatrists or psychologists.

Strengths of this analysis include using the microsimulation model that can represent the natural history of depressive disorder as a chronic episodic disease. It allowed us to track all patients as individuals taking into account the wide variation in the length and frequency of episodes. The efficacy data of antidepressants are from a meta-analysis that took into account unpublished data from pharmaceutical companies reported to the Food and Drug Administration, avoiding the publication bias that affects meta-analyses of published trials. The majority of published studies were conducted by pharmaceutical companies with a vested interest.

The main limitation of this study was the measurement of the health benefit for each of the treatment options. There is no information on the benefit of these interventions for major depression in Thailand. We therefore relied on data from international meta-analyses. The ES of interventions from clinical trials may not directly translate into effectiveness. The generalizability of the effectiveness measures, particularly for CBT, has not been established. Psychological interventions under routine health-care circumstances in Thailand may work differently from how they work in different countries because of differences in health services, culture, lifestyles, and beliefs [60]. The cost of CBT did not take into consideration starting-up costs, and so this can lead to an underestimation of the implementation costs in our study. If Thailand would choose to implement CBT as a treatment option for patients with major depression it would need to consider the cost of health personnel training and the cultural factors that may influence its effectiveness. We recommend future research on the efficacy and applicability of CBT or other psychosocial interventions in the Thai context.

The results of this cost-effectiveness analysis indicate that CBT could be a cost-effective treatment option in Thailand and that it potentially can be more effective than drug treatment of major depression, albeit under a series of assumptions regarding its efficacy in Thailand.

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