Cost-effectiveness of improved primary care treatment of depression in women in Chile

Dan Siskind, Ricardo Araya and Jane Kim

Background
Low- and middle-income countries lack information on contextualised mental health interventions to aid resource allocation decisions regarding healthcare.

Aims
To undertake a cost-effectiveness analysis of treatments for depression contextualised to Chile.

Methods
Using data from studies in Chile, we developed a computer-based Markov cohort model of depression among Chilean women to evaluate the cost-effectiveness of usual care or improved stepped care.

Results
The incremental cost-effectiveness ratio (ICER) of usual care

was I\$113 per quality-adjusted life-year (QALY) gained, versus no treatment, whereas stepped care had an ICER of I\$468 per QALY versus usual care. This compared favourably with Chile's per-capita GDP. Results were most sensitive to variation in recurrent episode coverage, marginally sensitive to cost of treatment, and insensitive to changes in health-state utility of depression and rate of recurrence.

Conclusions
Our results suggest that treatments for depression in low- and middle-income countries may be more cost-effective than previously estimated.

Declaration of interest
None.

Major depressive disorder is one of the leading causes of disease burden worldwide.[1] This burden is highest among the poorest populations, which also have the greatest barriers in accessing care.[2] *The Lancet* series on global mental health has underscored the growing need to identify how scarce resources can be used efficiently, effectively and feasibly in low- and middle-income countries.[3] Most depression treatment studies have been conducted in high-income countries.[4,5] However, a handful of studies carried out in low- and middle-income countries have evaluated the cost-effectiveness of depression treatments and these can be used to aid in policy decisions.[6] When there are limited empirical data, decision-analytic methods can be useful in informing policy decisions. In resource-poor settings with limited prospective data on disease burden and treatment effectiveness, a computer-based Markov model of depression allows us to extend information from empirical studies by extrapolating patterns beyond the time horizon of any one single study and can provide a formal framework for synthesising multiple data sources in an internally consistent and epidemiologically plausible way. Araya *et al*[7,8] conducted a randomised controlled trial to compare usual care with an improved treatment programme for depressed women on a low income in primary care in Santiago, Chile. Depression is a lifelong illness involving repeated relapse and remission and this clinical trial was based on a single episode of depression, thus limiting its capability to evaluate interventions over the long term. Using data from this clinical trial in Chile and other local sources, we evaluated the clinical benefits and cost-effectiveness of usual care and stepped care improved treatment programmes. We then compared our estimates with commonly cited benchmarks of cost-effectiveness for health interventions and those of a previous cost-effectiveness analysis for the treatment of depression.[9]

Method

Decision-analytic model

We modified a previously developed Markov cohort model of major depression[10] for use among women in Chile. The Markov

model follows a cohort of adult women through a series of clinically relevant health states, starting at age 18 throughout their lifetime (Fig. 1). At 6-month intervals, individuals can make the transition between mutually exclusive health states: no depression (i.e. well), depression (episodes 1–9), remission (i.e. well but with previous history of depression), chronic depression (after 9 episodes) and dead. Because of the inherent 'memoryless' property of Markov models, we included 19 depressive health states to keep track of nine consecutive episodes of depression and remission (18 health states), as well as chronic depression (1 health state), which can only be achieved after an individual experiences nine prior depressive episodes and remissions. The inclusion of these 'tunnel states' in the model allowed us to introduce memory of prior episodes, which affects probabilities of future events.[11] The incidence of depression was modelled using estimates of age-specific prevalence and duration of depression in Latin America. All individuals faced a probability of dying based on all-cause mortality, plus an increased risk of death by suicide in the depressed health states.

Input data

Table 1 shows the main model input parameters. To calculate the incidence of depression, we used estimates of prevalence from the Global Burden of Disease study from the region of the Americas–B (AMR–B), which includes Chile,[9] and assumed an average episode duration of 6 months.[12] Solomon *et al*[13] examined a cohort of individuals with a history of depression, both treated and untreated, and found a 10% risk of relapse in a 6-month period. We assumed that individuals had an increased risk of recurrence of 16% with each successive episode of depression.[13] Given this, participants in the model spent effectively all of their time in the depressed state after their tenth episode, and we therefore classified individuals as being in a chronically depressed state for the remainder of their lives after 10 episodes.

To estimate quality-adjusted life expectancy, we adjusted the time spent in each health state by a health-state utility weight. A health-state utility weight is a value between zero and one,
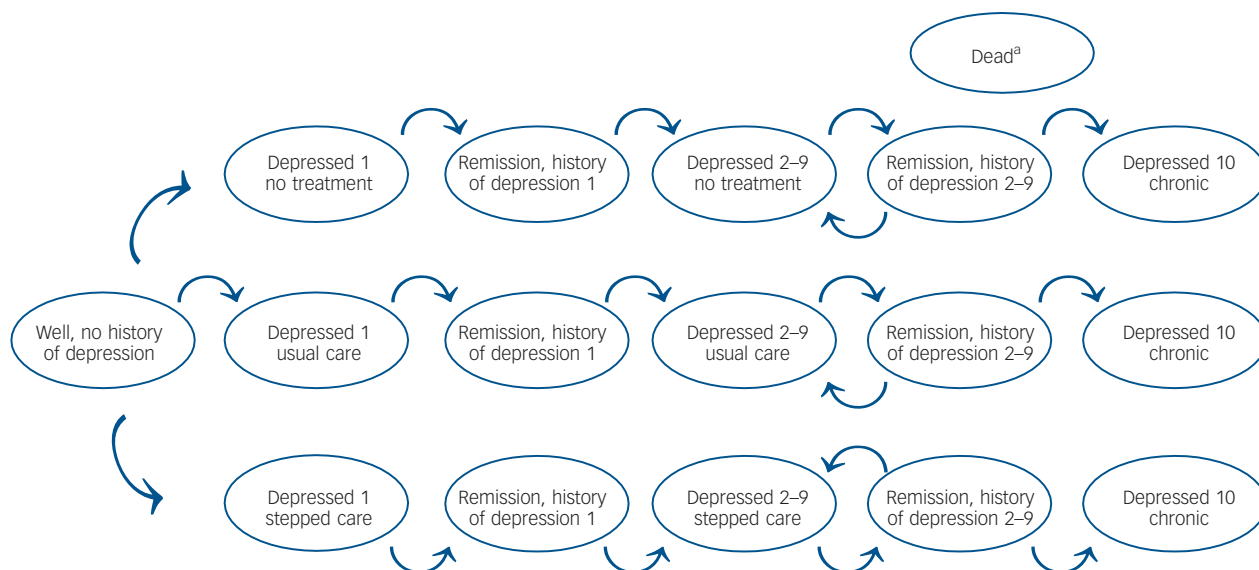
Fig. 1 Schematic of depression model.

Patients enter the model in the well state, with no history of depression. If they develop a first episode of depression, they enter one of three mutually exclusive treatment arms: 'no treatment', 'usual care' or 'stepped care'. After entering a treatment arm, patients make the transition between mutually exclusive states: 'depressed' and 'remission with a history of depression'. The number of episodes of depression (and remission), which affect the future probability of events, are tracked in the model using additional, unique 'tunnel' states, up to a patient's first nine episodes; after nine episodes, patients are considered to be in a chronic depressed state for their remaining lifetime.
a. In each cycle, all individuals face a probability of dying based on all-cause mortality, as well as excess mortality from suicide during depressive episodes.

corresponding to a quality of life adjustment for a given state of health, where one is perfect health and zero is death. We assumed that the baseline health state utility was 0.62 for the depressed state[9,14] and adjusted this utility weight by time to remission, based on data from the studies in Chile.[7,8] We assumed that the utility weight for those without depression decreased with age,[15] and that the age-specific and disease-specific utilities had a multiplicative relationship.

The formula for the derivation of utility was:

$$\text{Utility} = \frac{T_d}{26} \times 0.62 + \frac{26 - T_d}{26} \times U_{nd}$$

where T_d is mean time (in weeks) spent in the depressed state and U_{nd} refers to the age-adjusted utility of a person without depression.

All participants faced a risk of all-cause mortality from all health states based on region-specific life tables.[16] Individuals in the depressed state had an additional risk of death by suicide.[17] Baseline suicide rates in Chile were derived from Heerlein et al,[18] and we assumed that the relative risk of suicide in individuals with depression (no treatment) was 20 times greater than in non-depressed individuals;[19] depressed individuals in treatment were 1.8 times less likely to die by suicide than those not in treatment.[20]

Interventions

We evaluated the comparative costs and benefits of usual care and improved stepped care, compared with a baseline scenario of no treatment. In the base case, we assumed that treatment coverage for the initial episode of depression in Chile was 20% for both interventions.[2] We assumed that participants who had already sought treatment would be more likely to seek treatment in the future, resulting in higher treatment coverage for recurrent episodes. Given our estimate of initial episode coverage of 20%,[2] we assumed that participants who had received usual care would have a 50% chance of accessing treatment for future episodes. In the stepped care strategy, where participants were more adherent

with medication, we assumed individuals were more engaged in treatment and would be even more likely to return to treatment. We assigned them a 80% chance of accessing care for future episodes. Because of the lack of published data on treatment adherence for recurrent episodes, we sought expert opinion to validate our assumptions. We assumed that participants receiving usual care had the same likelihood of relapse as those receiving stepped care. Individuals receiving either treatment were less likely to relapse than those not in treatment by an odds ratio of 0.30.[21]

Data for effectiveness and costs of the two interventions in Chile were derived from studies by Araya et al,[7,8] in women who received care for depression through their primary care doctors. In these studies, women were randomly divided into two groups, one receiving usual care and the other receiving an improved stepped care package, as described previously. Individuals in the usual care group had, on average, 35 (95% CI 32–39) depression-free days in 6 months. Using the formula for derivation of utility noted above, we calculated a utility weight of 0.69 for usual care. Individuals in the stepped care group had 67 (95% CI 64–72) depression-free days in 6 months, resulting in a utility weight of 0.76

Intervention costs included service provision costs and medication costs (Table 2).[7] Participants in both intervention groups were able to see their primary care doctor and be referred to a psychiatrist if necessary. Mean visits refers to the mean number of visits participants made to each service provider during the course of the 6 month intervention. Individuals in the stepped care group also attended psychoeducational groups. Costs associated with this programme element included the costs of running the groups themselves, as well as the fixed costs of training group leaders, and the liaison between supervising psychiatrists, primary care physicians and non-medical mental health providers. Mean costs refers to the mean cost per participant over the course of the intervention of the service or medication. Participants in both treatment groups could receive psychopharmacology, which included antidepressants (tricyclic antidepressants (TCAs) and selective serotonin reuptake

Table 1 Model input parameters

Variable	Value	Range	Reference
Incidence of depression per 1000 population (females only)	20.2–86.0[a]	0.5–1.5[b]	Chisholm et al[9]
Duration of episode, months	6	–	Eaton et al[12]
Baseline rate of recurrence (every 6 months)	0.10	0.01–0.20	Solomon et al[13]
Increased risk of recurrence per additional episode	0.16	0.05–2.0	Solomon et al[13]
Odds ratio of relapse (treated v. untreated)	0.30	0.20–0.50	Geddes et al[21]
Treatment coverage for initial episode, %	20	20–50	Araya et al[2]
Treatment coverage for recurrent episodes, %			
Usual care	50	50–100	c
Stepped care	80	80–100	c
Utility of depression			
No treatment	0.62	0.40–0.80	Chisholm et al,[9] Stouthard[14]
Psychopharmacology treatment	0.69		Araya et al[7,8]
Stepped care treatment	0.76		Araya et al[7,8]
Relative risk of suicide (depressed v. well)	20	10–30	Harris & Barraclough[19]
Relative risk of suicide among depressed (treated v. untreated)	1.8	1.0–3.0	Isacsson et al[20]

a. Range represents upper and lower limits of age-specific values.
b. 0.5–1.5 times baseline.
c. Values based on unpublished expert opinion.

inhibitors (SSRIs)) and benzodiazepines. Medication use refers to the percentage of participants who reported taking a particular medication during the course of the 6-month intervention. Participants in the stepped care group reported higher rates of antidepressant use than the usual care group. This higher rate of antidepressant adherence contributed to the higher cost of stepped care. The cost of usual care per depressive episode was I\$51 and the cost of the stepped care programme per episode was I\$88.

Cost-effectiveness analysis

We conducted our analysis with all future costs and benefits discounted at an annual rate of 3%, following published guidelines on cost-effectiveness analysis.[22] All costs were converted from the local currency in Chile (Peso) and expressed in 2003 international dollars (I\$), in order to facilitate comparison across different settings and interventions. International dollars are a hypothetical currency that reflects each country's purchasing power relative to the US dollar.[23] In 2003, the purchasing power of US\$1 was 311 Peso for Chile.[24] We expressed effectiveness of treatments in terms of quality-adjusted life-years (QALY) to reflect disease morbidity and mortality. Incremental cost-effectiveness

ratios were calculated as the additional cost divided by the additional benefit of one strategy v. the next less costly strategy and were reported as cost per QALY gained. Although there is no consensus on an appropriate threshold for cost-effectiveness below which an intervention would be considered attractive value for money, we evaluated the strategies using a commonly cited threshold of per-capita gross domestic product[25] (GDP), the sum of all incomes earned by the production of goods and services within a nation in a given year divided by the population,[26] which was I\$9900 in Chile (2003).[27]

Results

Reduction in episodes of depression

The model generates estimates of life expectancy, number of episodes of depression and total lifetime costs for a birth cohort using the data from epidemiological studies, and studies on costs and effectiveness of treatment. Under an assumption of 20% initial treatment coverage and treatment-specific recurrent episode coverage, episodes of depression were reduced by 4.7% with usual care and 7.4% with stepped care over the lifetime of the cohort. If

Table 2 Intervention costs[a]

	Stepped care			Usual care		
	Usage		Costs in I\$, mean	Usage		Costs in I\$, mean
	Visits, mean[b]	Prescriptions, mean[c]		Visits, mean[b]	Prescriptions, mean[c]	
Service type						
Service providers						
Primary care consultation	4.7		47.25	4.5		45.09
Psychiatry consultation	0.3		5.93	0.3		5.75
Psychoeducational groups	7.3		5.92			
Psychoeducational group training[d]			7.50			
Psychoeducational group liaison[d]			13.08			
Medications, prescriptions						
Benzodiazepine		13	0.00		45	0.01
Antidepressant		80	2.24		56	0.61
Total costs			87.85			51.50

I\$, international dollars.
a. Table adapted from Araya et al.[7]
b. Mean visits refers to the mean number of visits participants made to each service provider during the course of the 6-month intervention.
c. Mean prescriptions refers to the mean number of prescriptions per participant that they reported taking during the course of the 6-month intervention.
d. Fixed cost.

initial treatment coverage is increased to 75%, reductions in episodes would increase to 14.0% for usual care and 22.3% for stepped care. If treatment coverage for recurrent episodes were doubled for both interventions, reductions would be 7.0% and 8.4%, respectively.

Incremental cost-effectiveness ratios

The model projected that 18-year-old Chilean women who did not receive any treatment for any lifetime depressive episodes would live, on average, an additional 20.69 discounted QALYs. Quality-adjusted life expectancy could increase to 20.82 QALYs with long-term usual care and 20.91 QALYs with long-term stepped care, translating to gains of 32 days and 48 days, respectively, when compared with no treatment. Treatment with usual care was associated with a total lifetime discounted cost of I$15 per person and a cost per QALY of I$113, compared with no treatment. In contrast, treatment with stepped care would cost an additional I$26 per person and result in an incremental cost of I$468 per QALY gained, compared with usual care (Table 3).

Lifetime costs for cohort

The results of our analysis imply that over the lifetime of the current cohort of 18-year-old women in Chile (approximately 130 000),[28] treatment of depression with usual care would cost I$1 950 000; treatment with stepped care would cost an additional I$3 380 000.

Sensitivity analysis

We conducted a variety of sensitivity analyses to assess the stability of results across a range of uncertain model assumptions. The base case cost-effectiveness results were sensitive to assumptions made about achievable recurrent episode coverage. When recurrent episode coverage for usual care increased to 70% (from 50% in the base case), the cost per QALY for this strategy decreased to I$80; in contrast, the incremental cost effectiveness ratio (ICER in I$ per QALY) for stepped care increased to I$1190, compared with usual care. When coverage of usual care for recurrent episodes was close to stepped care (78%), the ICER for stepped care increased to I$5130. When coverage of stepped care for recurrent episodes was decreased to 52% (from 80% in the base case), the ICER for this strategy increased to I$8210.

Base case results were also marginally sensitive to cost of treatment. When the cost of stepped care was doubled, its ICER reached nearly I$1000. It was not until this cost was increased 20-fold that the ICER for this strategy exceeded I$9900. The cost of usual care did not increase above I$500 per QALY across a plausible range of values and required a fourfold increase to exceed the lifetime cost of stepped care treatment.

Results were insensitive to changes in health-state utility of depression and rate of recurrence. These findings make sense given that the underlying influences of both interventions on these variables are similar. The main difference in strategy performance occurred when the rates of coverage for recurrent episodes were varied.

Discussion

Using Chile's per-capita GDP as a threshold for cost-effectiveness, the improved stepped care programme should be considered very cost-effective in Chile. This result was stable over most assumptions; only when recurrent treatment coverage for stepped care was decreased to the same level as usual care (i.e. 50%) did the ratio approach the 2003 per-capita GDP benchmark of I$9900.

If stepped care is not a viable option in Chile for any reason, usual care would also provide good value for money. When compared with no care, the ICER of usual care was I$113 per QALY gained. However, in order to maximise benefits, the strategy with the highest cost-effectiveness ratio below the society's willingness to pay for a QALY[22] would be selected. Thus, if stepped care is equally available, it would be preferred over usual care as the ICER for stepped care is below the willingness-to-pay threshold of Chile's per capita GDP.

Cost-effectiveness of other health interventions

It is important to note the distinction between value for money (i.e. cost-effectiveness) and the financial impact (i.e. affordability) of interventions. Although both treatment strategies were considered to be cost-effective options, the lifetime cost of usual care and stepped care for the current cohort of 18-year-old women in Chile is I$1.9 million and I$5.3 million, respectively. Considering the competing demands of other health interventions for resources, with a health budget of I$9.6 billion in Chile in 2003, it must be determined whether these interventions are affordable.

To place our results in the context of other health interventions competing for similar resources, we compared our estimates of cost-effectiveness with those of other interventions for chronic diseases that are priorities in Latin America, including cardiovascular disease and diabetes mellitus. Using a Markov model of cardiovascular disease in low- and middle-income subregions of the world, Gaziano et al[29] estimated that a medication regime for the secondary prevention of cardiovascular disease cost I$393 per disability-adjusted life-year (DALY) averted in Latin America. In contrast, a treatment protocol for intensive glycaemic control in people with diabetes mellitus in Latin America would cost I$4049 per QALY gained.[30] Using both examples to gauge the value of treatments for depression, we found that stepped care would comparably provide good value for money.

Cost-effectiveness of other evaluations of depression treatment

Araya et al[7] made an estimate of the incremental cost per QALY gained when the stepped care programme was used in place of

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Table 3 Cost-effectiveness results[a]

Treatment strategy	Reduction in lifetime episodes of depression, %	Quality-adjusted days gained	Total average life-expectancy, QALY	Total average life-time costs, I$	ICER,[b] I$/QALY
No treatment	–	–	20.69	0	–
Usual care	4.7	32	20.82	15	113
Stepped care	7.4	48	20.91	41	468

I$, International dollars; QALY, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio.
a. Analysis assumes 20% coverage for initial treatment, 50% adherence to usual care and 80% adherence to stepped care.
b. Incremental cost-effectiveness ratios (ICER) were calculated as the additional cost divided by the additional benefit of one strategy v. the next less costly strategy.

usual care. Based on an assumed improvement in utility from 0.6 to 0.8 on recovery from symptomatic depression, they estimated that the ICER would range from I$683 to $1365 per QALY gained. These results are slightly higher than, but within a reasonable range of, our base case results for the stepped care programme.

In a similar model-based analysis of cost-effectiveness of multiple treatments for depression in 14 world regions, including those encompassing Chile (AMR-B), Chisholm et al[9] found that the individual-level costs for usual care (psychopharmacology) were I$135 (TCAs) and I$169 (SSRIs) with an average ICER of I$1805 (TCAs) and I$2136 (SSRIs) per DALY averted. Stepped care (psychopharmacology plus 'proactive' care) was estimated to have an individual-level cost of I$176 (TCAs) and I$217 (SSRIs) and an ICER of I$2998 (TCAs) and I$4104 (SSRIs) per DALY when compared with TCAs alone. Part of the discrepancy in findings is attributable to their conservative estimates of utility associated with treatment. Whereas Chisholm et al[9] assumed that usual care increased health-state utility to 0.65 during a 6-month episode of depression and stepped care increased utility to 0.67, we assumed a utility of 0.69 for usual care and 0.76 for stepped care derived from empirically obtained data.[8] Fluoxetine came off patent in 2002, drastically lowering the cost of this SSRI. This cost reduction may not have been fully captured in the Chisholm et al[9] study.

We recently conducted a study on the cost-effectiveness of group psychotherapy for depression in Uganda[10] using a similar Markov model of depression. We found that group psychotherapy with booster sessions had an ICER of $1150 per QALY when compared with no treatment. Although this intervention was considered to be very cost-effective when compared with Uganda's per capita GDP the results from both studies may suggest that psychotherapies in low- and middle-income countries may not be as cost-effective as pharmacotherapy.

Possible explanations for cost-effectiveness of stepped care

Rates of recovery in Araya et al's[8] study were found to be higher when compared with other similar studies. Araya et al also noted that participants in the stepped care group were more likely to be adherent to medication when compared with usual care.[8] A study in the USA found that individuals in stepped care were more likely to refill prescriptions than those in the care as usual group by an odds ratio of 1.91 (CI 1.37–2.65).[31] This increase in medication adherence partly explains why stepped care had a higher effectiveness with an increased cost. It is also possible that treatments that incorporated additional human contact, such as stepped care (which involved a psychoeducation group), would have an additional effect of engaging individuals and aiding in the amelioration of depression when compared with similar treatments without this component.

Limitations

Our study had several limitations. We relied on studies from high-income countries for some of our data on natural history and recurrence risk. These estimates may not be entirely applicable to the setting of Chile but there were no country-specific data to inform these parameters. As there are only very few published studies on effectiveness of treatment of depression in low- and middle-income countries[6] there is also the risk of a publication bias. The data that we used as model inputs from Chile were from a relatively small (n = 240) single-site study but this was the only one available from Chile.

We did not model maintenance therapy. Guidelines for the treatment of depression recommend treatment for 1 year following an initial episode of depression and for 3 years following each recurrent episode.[32] Given the higher rates of adherence to medication in the stepped care group it is likely that they would be more adherent to maintenance treatment, and have lower rates of relapse.[33] Given the relatively low cost of antidepressants, this would decrease the ICER of stepped care v. usual care.

The psychopharmacology arm of this study was based on the use of generic preparations. There have been some reservations made about the use of generics but their effectiveness has been proven to be equivalent to patented formulations.[34] Nonetheless industry standards in low- and middle-income countries vary and quality control in the manufacture of these formulations is often unknown.

We did not model for the medical comorbidities of depression. However, it is known that people with depression are two to four times more likely to develop cardiovascular disease,[35] increasing the risk of overall morbidity. Nor did we explicitly model sub-syndromal depression, which can also significantly affect quality of life[36] and increase days lived with disability.[37] As comorbid illness affects people later in life, the magnitude of the additional health-state disutility's effect on lifetime QALYs would be small, making it unlikely that our results would change qualitatively. Any change in the results would likely show that both of the treatments were more attractive than our current estimates, but the incremental value of one strategy v. another would probably not change, as both interventions would be similarly affected by the inclusion of comorbid illness. Further Markov models of depression would benefit from the inclusion of comorbidity.

Cultural and gender contexts

The experience of depression, help-seeking behaviours and professional practices are influenced by culture. Thus it is difficult to know to what extent these findings can be generalised to other settings.[38] Nonetheless regional countries with similar cultures and health services may find these results of interest.

The economic value of women's time lost to depressive illness is often neglected. Many of the women in Araya et al's study[8] stated that they were housewives, but in reality worked in the informal sector. Future studies that quantify women's opportunity costs in much more detail are needed, so that these important, non-trivial factors can be incorporated into economic analyses of the cost of depression.

Global policy implications

Despite untreated unipolar depression remaining a major cause of morbidity globally, there is reason to be optimistic about improving quality of and access to treatment in deprived communities. The results of our analysis may aid in the international campaign for access to appropriate treatment for depression in low- and middle-income countries. Further research into effectiveness of scalable depression treatment programmes in other resource-poor settings could be reviewed and added to our models to update and revise our cost-effectiveness estimates, and further aid in decision-making for mental health resource allocation.

Dan Siskind, MBBS, MPH, FRANZCP, Queensland Center for Mental Health Research, University of Queensland School of Population Health and Division of Mental Health, Princess Alexandra Hospital, Brisbane, Australia; Ricardo Araya, PhD, Academic Unit of Psychiatry, University of Bristol, Bristol, UK; Jane Kim, PhD, Center for Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, Boston, Maryland, USA

Correspondence: Dan Siskind, School of Population Health, University of Queensland, Queensland Center for Mental Health Research, Level 3 Dawson House, The Park, Wacol, QLD 4076, Australia. Email: dan_siskind@qcmhr.uq.edu.au

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