**ACE Prevention Briefing Paper: Drugs and psychological interventions for the treatment of depression**

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## 1.1 Introduction

This paper represents a short version briefing paper which details the cost-effectiveness of several interventions available for the **treatment** of adult depression. In a separate briefing paper Cathy Mihalopoulos presents the cost-effectiveness evaluation of interventions aimed at the **prevention** of adult depression.

Similar interventions were evaluated in the ACE-Mental Health project for the treatment of adult depression, where the base case was Australia in the year 2000 (Vos, Corry et al. 2005). Since that study, a number of structural changes to the delivery of psychotherapies has occurred such that psychologist services are now subsidised by the Commonwealth Government on the Medicare schedule. In order to be policy relevant in 2008, we have decided to model the provision of psychological therapies in the reference year of 2003 under the new funding arrangements.

An important study has been recently published which indicates publication bias has significantly affected previous meta-analyses of published drug trials (Kirsch, Deacon et al. 2008). In a sample of trials reported by industry to the Federal Drug Administration in the US prior to approval of the newer generation of antidepressant drugs, a lower effect size was found and though not pooled as such by Kirsch, an obvious lower effect size for unpublished trials was identified. We have assumed that a similar publication bias applies to trials reporting on relapse rates while on treatment, and we adjusted the relative risk of relapse accordingly.

The interventions have been evaluated for incremental cost-effectiveness in the reference year of 2003 in line with the protocol for the ACE Prevention project (Vos, Carter et al. 2008).

## 1.2 Definition of intervention/s

The selected interventions for adult depression include:

1. drug treatment with TCAs for acute major depressive episodes plus a six month continuation phase after remission of symptoms;
2. drug treatment with SSRIs for acute major depressive episodes plus a six month continuation phase after remission of symptoms;
3. CBT treatment of acute major depressive episodes consisting of 12 sessions provided by a psychologist, to individuals **or** in a group;
4. bibliotherapy for acute episodes;
5. five years maintenance treatment with TCAs following an acute episode;
6. five years maintenance treatment with SSRIs following an acute episode; and
7. a maintenance variant of CBT with booster sessions over a period of five years provided by a psychologist, to individuals **or** in a group.

We model the impact of the acute episode interventions (options 1–3) in Australians experiencing at least one episode of major depression in the year 2003 (571,000) who sought care (337,000) but did not receive an evidence-based treatment (136,000). These estimates are based on the 1997 Survey of Mental Health and Well Being (SMHWB) (Australian Bureau of Statistics 1998). The criterion for seeking care was consulting for a mental health problem with a psychologist, psychiatrist, GP, surgeon, social worker, mental health team worker or an admission to hospital. We defined evidence-based treatment as a minimum of three such consultations and having received medication and/or CBT. We assume that only 15% of patients are likely to take up bibliotherapy. We model the impact of maintenance interventions (options 4–6) in all people seeking care for depression in the year 2003 (337,000) assuming maintenance treatment is not part of current practice.

## 1.3 Current practice

The comparator to all interventions is current practice as they are aimed at people who meet the above criteria and are not receiving evidence-based medicine or maintenance therapies.

## 1.4 Efficacy/effectiveness of intervention/s

The study by Kirsch et al (Kirsch, Deacon et al. 2008) provides the estimate of the effectiveness of drug interventions. This is a recent meta-analysis evaluating the effectiveness of SSRI drug interventions on the reduction of depressive symptoms. This meta-analysis found an effect size of SSRIs in comparison to placebo of 0.32 (95% CI 0.25, 0.40). Other meta analyses consistently show an absence of difference in efficacy between TCAs and SSRIs (Anderson 2000; Geddes, Freemantle et al. 2000). Kirsch's estimate of effect size is 42% lower than that previously used in the ACE Mental Health studies which was based on the meta-analysis of Trinidade et al (Trinidade and Menon 1997).

## 1.5 Modelling to health outcomes

The method relies on an Australian valuation study which quantified a mean disability weight (DW) change for each standard deviation (SD) change in severity of depression (Sanderson, Andrews et al. 2004). As the effect size (or 'standardised mean difference') quantifies the impact of an intervention in SD units, the product of the effect size and the mean DW change per SD represents the health gain. Reductions in the DW are only applied to the time from the commencement of the intervention taking into account a lag to treatment seeking. We model that those not adhering to treatment gain no health benefit although they can incur some costs. For bibliotherapy we model health gain during the acute episode only. This may well be an underestimate as it is not unlikely that this self-help variant of CBT also has benefits beyond the acute episode. We make this decision because we have no direct evidence for a sustained benefit and because the cost-effectiveness ratio is very favourable anyway due to the very low cost of the intervention.

During the continuation and maintenance treatment periods following an acute episode we assume that the reduction in risk of recurrence or relapse can be applied to the average time spent in depression. This average time was estimated by simulation methods using lognormal distributions of the duration of episodes and the time to the next episode derived from follow-up studies of community samples of people with depression.

## 1.6 Costs of interventions and offsets

The costs of the drug interventions include medical and pharmaceutical costs. We assume the same mix of providers as reported in the SMHWB, prescribing and supervising drug treatment (56% general practitioner (GP) only, 10% psychiatrist only and 33% GP plus psychiatrist). We take into account weekly visits in the first month, monthly visits for two months and then every three months for review. For those seeing both a GP and a psychiatrist we include one initial GP visit for referral, weekly sessions with a psychiatrist for one month and then fortnightly for another month before being referred back to the GP for further monitoring and management once every 1-2 months. We assume that cases not adherent with drug treatment accrue similar costs as those on non-evidence based treatments. Pharmaceutical costs are based on 2003 PBS data for total scripts and cost to Government. It has been assumed that the ratio of private individuals to Government costs

for pharmaceuticals is the same as previously analysed for the year 2000 within the ACE Mental Health project.

The costs of the cognitive behavioural therapy intervention included medical costs only performed by a psychologist at rates determined by Medicare, following an initial GP visit for referral. The number of sessions with a psychologist modelled, is 12 for the first year.

Bibliotherapy is modelled as one long and two short visits to a GP and the purchase of a book.

Depressed patients who receive non-evidence based treatment under current practice are costed for the mean number of visits to a GP (4.2), psychiatrist (0.3) and psychologist (2.2) as observed in SMHWB.

The cost-offsets of the intervention were defined as the costs associated with the treatment of Major Depressive Disorder with non-evidence based medicine. The costs were estimated from the treatments identified in the SMHWB.

Time and travel costs for patients have not yet been assessed for any interventions.

## 1.7 Key assumptions

Some of the key assumptions of the current analysis include:

- The publication bias identified by Kirsch et al (Kirsch, Deacon et al. 2008) which exaggerates the benefits of drug therapy similarly applies to the relative risk of relapse while on treatment and following treatment for depression.
- Psychological treatments have Medicare item numbers as from 2007 (deflated to 2003 values).
- The SMHWB accurately identifies current practice in 2003.

## 1.8 Uncertainty and sensitivity analysis

To incorporate the uncertainty associated with all cost and outcome data we use Monte Carlo simulation modelling and present uncertainty ranges as well as point estimates for benefits, costs, cost offsets and cost-effectiveness ratios. Details of the parameters varied in the uncertainty analysis are detailed in Appendix 2. We use @RISK software which allows multiple recalculations of an Excel spreadsheet, each time selecting a value from the pre-specified distributions of the input variables. We present 95% uncertainty ranges for the output variables bounded by the 2.5 and 97.5 percentiles of the 4000 iterations of the model.

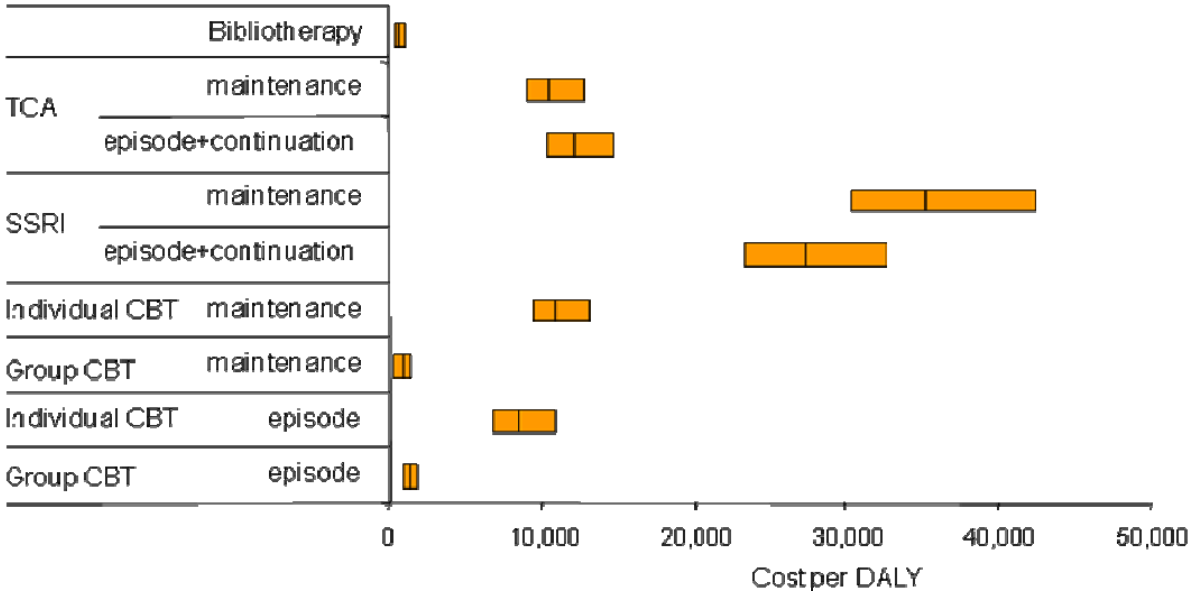
Sensitivity analysis is a useful addition to probabilistic uncertainty analysis, as it allows the impact of individual key design factors of an intervention to be assessed. Sensitivity testing of key input parameters was conducted with the CBT interventions since CBT can be provided to individuals or to a group of individuals. We explore in univariate sensitivity testing, the impact of the mode of delivery on the cost-effectiveness ratios for CBT.

## 1.9 Results

### *1.9.1 Technical analysis (incremental cost-effectiveness ratios)*

All depression therapies examined are incrementally cost-effective at less than $50,000 per DALY. Bibliotherapy is the most cost-effective at $1,000 per DALY, followed by group CBT as a maintenance strategy then group CBT for episodes. The cost-effectiveness of individual episodic or maintenance CBT is similar to episodic or maintenance therapy with TCAs at around $10,000 per DALY. Episodic treatment with the relatively expensive SSRIs is more cost-effective than maintenance therapy.

**Figure 1: Comparison of ICERs for each of the depression interventions**




Note: continuation =6 months therapy following an acute episode. maintenance= five years therapy following an acute episode

- Pharmacological interventions

TCAs are more cost-effective than SSRIs and maintenance therapy on TCAs is more cost effective than episodic treatment, although the uncertainty intervals overlap. The alternative maintenance therapy with SSRIs is less favourable than episodic therapy but is still well below the $50,000 threshold at $35,000 ($30,000-$42,000) However, if the ICER of SSRIs is measured compared to TCAs rather than current practice, the result is much less favourable at $540,000 ($300,000 - $14,000,000) for episodic treatment and $610,000 ($360,000-$16,000,000) for maintenance treatment. Maintenance therapies are associated with the largest amount of health gain.

**Figure 2** Scatter plot of 4000 uncertainty iterations with $50,000 per DALY averted threshold cut-off

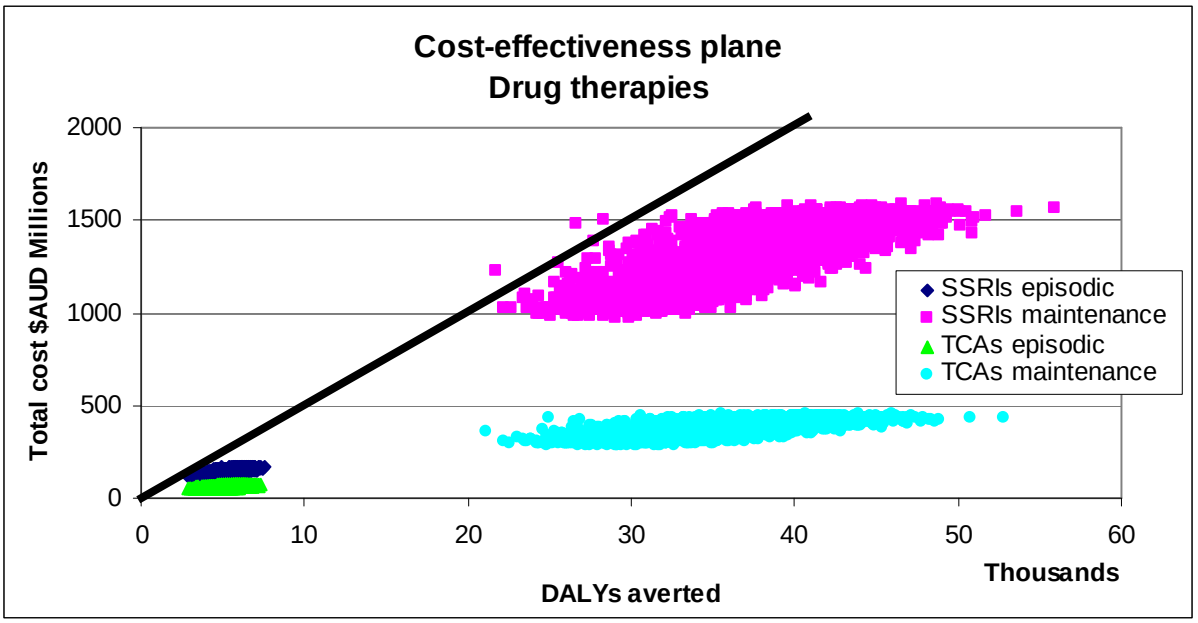
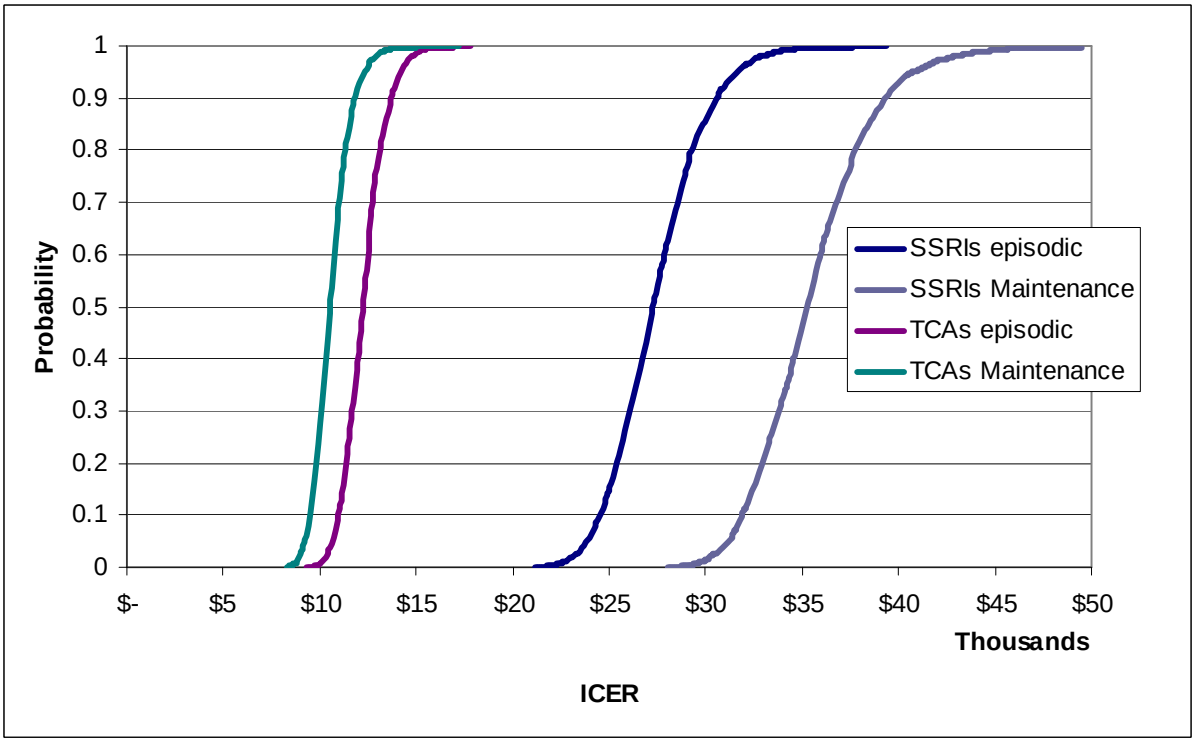



Figure 3 Acceptability curve (including cost offsets) drug therapies




The ICERS and costs of the pharmaceutical interventions, are detailed in Table 1

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**Table 1 Results of reference case analysis for pharmaceutical interventions**

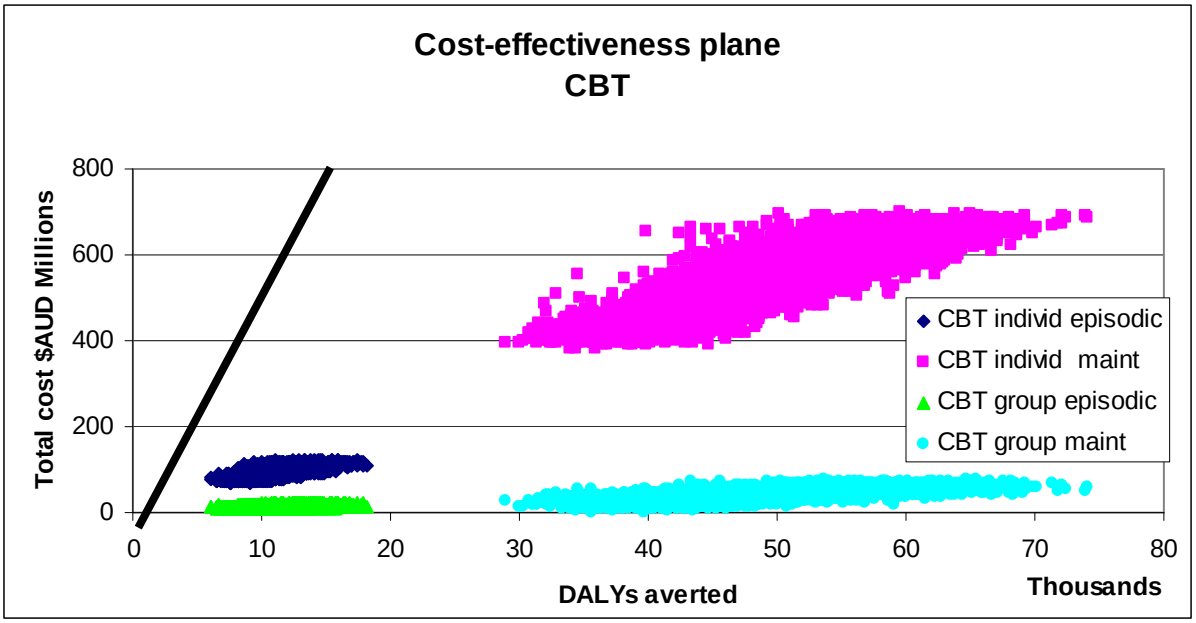
| | TCAs episodic | TCAs maintenance | SSRIs episodic | SSRIs maintenance |
|---|---|---|---|---|
| DALYs averted | 4,900 (3,700 – 6,300) | 35,000 (27,000 – 44,000) | 5,000 (3,700 – 6,600) | 36,000 (27,000 – 46,000) |
| Cost of Intervention | | | | |
| Cost to Government (AUD Million) | 55 ( 46 – 64 ) | 410 ( 340 – 480 ) | 120 ( 99 – 140 ) | 1,200 ( 950 – 1,400 ) |
| Cost to Patient (AUD Million) | 15 ( 12 – 17 ) | 120 ( 98 – 140 ) | 27 ( 23 – 32 ) | 260 ( 210 – 310 ) |
| Cost offsets (AUD Million) | 9 ( 6 – 14 ) | 160 ( 130 – 190 ) | 10 ( 6 – 15 ) | 160 ( 130 – 190 ) |
| Net costs (AUD Million) | 60 ( 52 – 70 ) | 370 (300 – 440) | 140 ( 110 – 160 ) | 1,300 (1,000 – 1,500) |
| **ICER (with cost-offsets) (AUD per DALY)** | **12,000 ( 10,000 – 15,000)** | **11,000 ( 9,000 – 13,000)** | **27,000 ( 23,000 – 33,000)** | **35,000 ( 30,000 – 42,000)** |
| **ICER (without cost-offsets) (AUD per DALY)** | **14,000 ( 12,000 – 17,000)** | **15,000 ( 13,000 – 18,000)** | **29,000 ( 25,000 – 35,000)** | **40,000 ( 34,000 – 48,000)** |

Median point estimate (95% uncertainty interval) to two significant digits

- Psychological interventions

CBT episodic or maintenance therapy was found to be cost-effective with 100% of the uncertainty iterations falling below $50,000 per DALY (Figure 4). Maintenance therapy is slightly less cost-effective than episodic treatment, for individuals, while for groups of patients, maintenance therapy is slightly more cost-effective than episodic therapy. The ICERs for group therapy are much lower than for the equivalent therapy provided to individuals.

**Figure 4 Scatter plot of 4000 uncertainty iterations with $50,000 per DALY averted threshold cut-off**




Bibiliotherapy is the most cost-effective intervention with all iterations of the ICER falling below $1,000 per DALY (**Figure** 5), but the total DALY gain is less.

**Figure 5 Scatter plot of 4000 uncertainty iterations with $50,000 per DALY averted threshold cut-off**

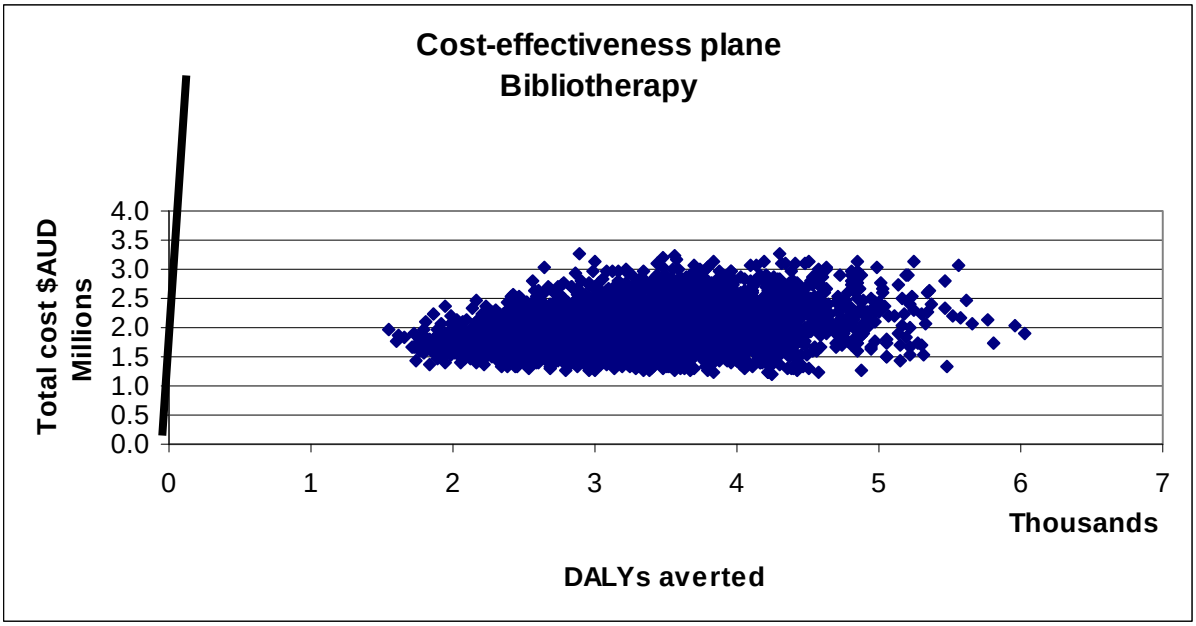
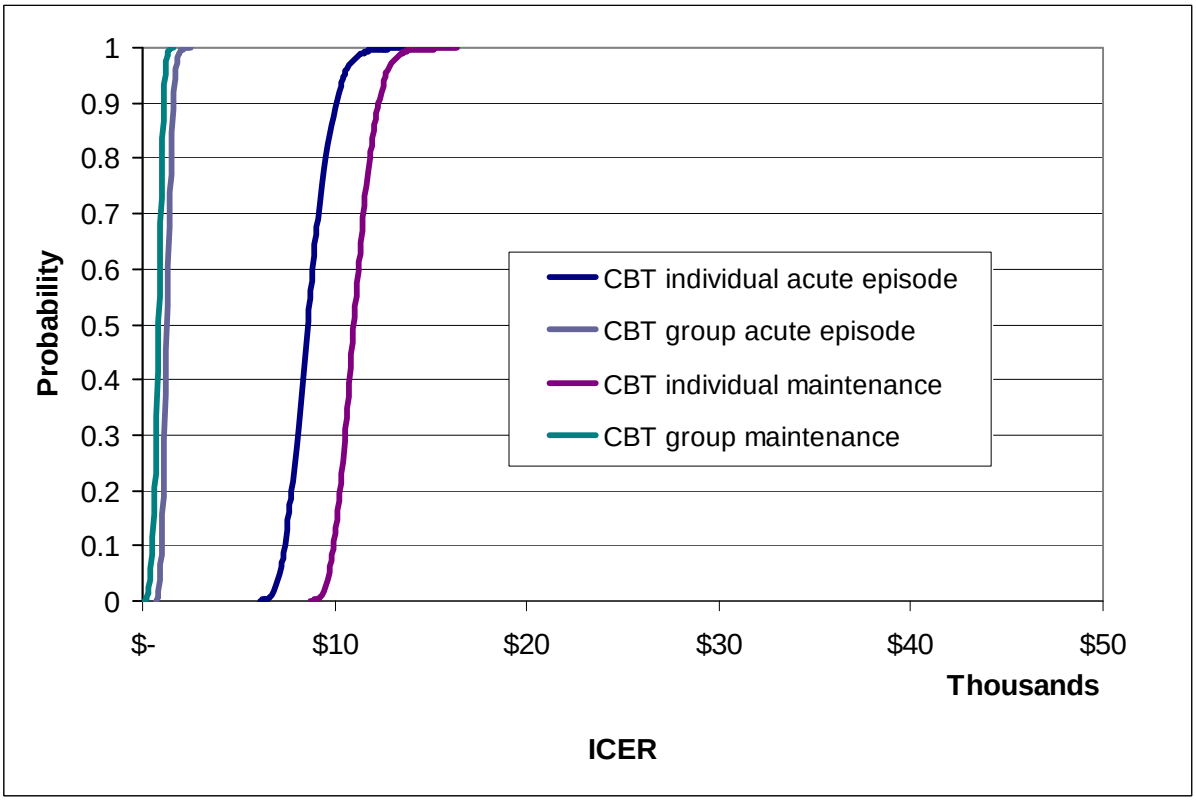



**Figure 6 Acceptability curve of psychological interventions (including cost offsets)**




The ICERS and costs of the Cognitive Behavioural Therapy and Bibliotherapy interventions, are detailed in Table 2

**Table 2 Results of reference case analysis for CBT interventions and Bibliotherapy**

| | Individual CBT episodic | Group CBT episodic | Individual CBT maintenance | Group CBT maintenance | Bibliotherapy |
|---|---|---|---|---|---|
| DALYs averted | 11,000 (7,600 – 15,000) | 11,000 (7,600 – 15,000) | 49,000 (35,000 – 65,000) | 49,000 (35,000 – 65,000) | 3,200 (2,000 – 4,800) |
| Intervention cost | | | | | |
| Cost to Government (AUD Million) | 91 ( 72 – 110 ) | 23 ( 18 – 28 ) | 610 ( 480 – 740 ) | 180 ( 140 – 210 ) | 3.5 ( 2.6 – 4.5 ) |
| Cost to Patient (AUD Million) | 14 ( 11 – 17 ) | 1.7 ( 1.5 – 1.9 ) | 91 ( 72 – 110 ) | 27 ( 21 – 32 ) | 2.5 ( 1.5 – 3.7 ) |
| Cost offsets (AUD Million) | 10 ( 6 – 16 ) | 10 ( 6 – 16 ) | 160 ( 130 – 190 ) | 160 ( 130 – 190 ) | 4.0 ( 2.3 – 6.3 ) |
| Net costs (AUD Million) | 95 ( 75 – 120 ) | 14 ( 9 – 20 ) | 540 ( 410 – 670 ) | 42 ( 14 – 68 ) | 2.0 ( 1.4 – 2.8 ) |
| **ICER (with cost-offsets; AUD per DALY)** | **8,600 ( 6,900 – 11,000)** | **1300 ( 870 – 1,800)** | **11,000 ( 9,500 – 13,000)** | **850 ( 360 – 1,200)** | **620 ( 380 – 950)** |
| **ICER (without cost-offsets; AUD per DALY)** | **9,500 ( 7,700 – 12,000)** | **2,200 ( 1,800 – 2,800)** | **14,000 ( 12,000 – 17,000)** | **4,200 ( 3,600 – 5,000)** | **1,900 ( 1,400 – 2,700)** |

Median point estimate (95% uncertainty interval) to two significant digits

### *1.9.2 Second stage filter analysis*

Second stage filter considerations for all pharmacological and psychotherapy interventions are presented in section 1.12. The main issues are around acceptability to clinicians (GPs and psychiatrists) of a shift towards a greater emphasis on brief structured psychotherapy of a CBT nature versus the currently dominant treatment strategy of prescribing drugs. When similar analyses were done for the ACE-Mental Health study, two main issues were identified that may impede the wider implementation of a recommendation to advise a greater emphasis on psychotherapy for depression: a limited workforce and the absence of financial reimbursement. The latter has been resolved after the introduction a couple of years ago of a Medicare rebate scheme for brief psychotherapy interventions by psychologists in primary care. However, a limited workforce trained in CBT or comparable effective brief psychotherapy would become apparent if a greater shift away from drug treatment to psychotherapy would occur. This would become even more the case if brief psychotherapy were also to be prescribed to patients with other mental disorders such as anxiety or sub-syndromal depression where evidence also indicates that CBT is a cost-effective approach.

## 1.10 Discussion

All interventions for major depression examined have a favourable incremental cost-effectiveness ratio (ICER) under Australian health service conditions. The major limitations and strengths of the analysis have been documented in (Vos, Corry et al. 2005). This analysis adjusts downwards the benefits of drug therapies that may have been affected by publication bias as indicated by the new meta-analysis performed by Kirsch et al. A comparison of the cost-effectiveness ratios published in the ACE Mental Health study shows that the comparable pharmacological interventions are now half as cost-effective as previously thought. The CBT interventions provided to individuals are more expensive and less cost-effective under the new funding arrangement through Medicare, while still comparing favourably to TCAs and especially favourably compared to SSRIs. Group based CBT is similar in cost-effectiveness with the ACE Mental health results.

Time and travel costs are unlikely to greatly change the cost-effectiveness ratios of the pharmacological interventions but will add costs to the psychological interventions and reduce their relative cost-effectiveness against the drug therapies.

## 1.11 References

Anderson, I. (2000). "Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability." Journal of Affective Disorders **58**: 19-36.

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## 1.12 Second stage filter analysis summary (appendix)

**Table 3: Second stage filter summary**

| Cost per DALY | Strength of evidence | Equity | Acceptability | Feasibility | Sustainability | 'other effects' |
|---|---|---|---|---|---|---|
| **Drug therapy:**<br>Episodic TCAs<br>W/out Cost offsets: 14,000<br>With Cost offsets:12,000<br>Episodic SSRIs<br>W/out Cost offsets: 29,000<br>With Cost offsets: 27,000 | Sufficient evidence of adequate quality. Meta analysis of multiple published and unpublished trials | No important equity issues | Issues include:<br>Reluctance by clinicians to prescribe TCAs due to perception of greater side-effects ( unsupported by trial data)<br>Pressure on clinicians to prescribe newer drugs | Feasible within current workforce and institutional arrangements: | No important issues | Positive: Positive family effects (such as impact on potential carers etc).<br>Negative: Side- effects of medication exist |
| Maintenance TCAs<br>W/out Cost offsets: 15,000<br>With cost offsets: 11,000<br>Maintenance SSRIs<br>W/out Cost offsets: 40,000<br>With cost offsets: 35,000 | | | Worries of consumers about side-effects of long-term drug treatment strategies<br>Policy makers may be reluctant to endorse long-term drug treatment strategies (especially SSRIs), as there are already great pressures on the PBS budget | | | |

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| Cost per DALY | Strength of evidence | Equity | Acceptability | Feasibility | Sustainability | 'other effects' |
|---|---|---|---|---|---|---|
| **Decision point** | Very cost effective and TCAs more than SSRIs | | Significant issues | | | |
| **Cognitive Behavioural Therapy**<br>Episodic Individual<br>W/out Cost offsets: 9,500<br>With cost offsets: 8,600<br>Episodic Groups<br>W/out Cost offsets: 2,200<br>With cost offsets: 1,300<br>Maintenance Individual<br>W/out Cost offsets: 14,000<br>With cost offsets: 11,000<br>Maintenance Groups<br>W/out Cost offsets: 4,200<br>With cost offsets: 840 | Sufficient evidence of adequate quality, noting however that there are:<br><br>Few trials in people from Non-English speaking backgrounds<br><br>Few trials for providers other than psychologists<br><br>No trials among the indigenous population | Moderate equity concerns require attention:<br><br>Appropriateness for minority groups<br><br>Access for rural/remote consumers in non-metropolitan areas | Some issues that require resolution:<br><br>Acceptance of treatment by clinicians and consumers<br><br>Acceptance of a shift away from pharmacological treatments | Possible but challenging to implement in the short term:<br><br>Ensuring an adequate workforce of appropriately trained and accredited providers with adequate geographic distribution.<br><br>The Commonwealth government has recently introduced a reimbursement scheme for brief psychotherapy interventions or depression taking away a major barrier to the successful uptake of this intervention | No important issues | Positive:<br>Positive family effects (such as impact on potential carers etc).<br><br>Negative: |
| **Decision point**: | **Australian evidence in** | | **May be important acceptability concerns** | **Workforce** | | |

| Cost per DALY | Strength of evidence | Equity | Acceptability | Feasibility | Sustainability | 'other effects' |
|---|---|---|---|---|---|---|
| | **target population required** | | **to all key stakeholders of intervention** | | | |
| **Bibliotherapy**<br><br>**Without Cost offsets: 1,900**<br><br>**With cost offsets: 620** | Sufficient evidence | Minor equity issues;<br><br>likely to appeal to those with higher levels of literacy and socioeconomic status | No important issues of acceptability | No feasibility issues | No important issues of sustainability | Positive: Positive family effects (such as impact on potential carers etc). |
| **Decision point**: | **Very cost effective** | | | | | |

PBS, Pharmaceutical Benefit scheme; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant.

## APPENDIX 1 Model input parameters and sources of information

**Table 1: Uncertainty parameters used in the simulation analysis**

| Parameter | Values | Uncertainty distribution | Source |
|---|---|---|---|
| RR suicide in prevalent depression | 20.4 (SE 1.1) | Normal | (Vos, Corry et al. 2005) |
| RR suicide on treatment vs not on treatment | 1.8 (SE 0.1) | Normal | (Vos, Corry et al. 2005) |
| Effect size | | | |
| Antidepressant drugs | 0.32 (0.25-0.40) | Triangular | (Kirsch, Deacon et al. 2008) |
| CBT | 0.77 (0.44-1.10) | Triangular | (Vos, Corry et al. 2005) |
| Bibliotherapy | 0.98 (0.62-1.35) | Triangular | (Vos, Corry et al. 2005) |
| RR relapse during 6 months continuation of drug treatment | 0.66 (SE 0.147) | Normal | Assumed similar attenuation of effect, as reported in Kirsch et al 2008 for episodic treatment |
| RR relapse during maintenance drug treatment | 0.67 (SE 0.053) | Normal | |
| RR relapse during 18 months following CBT | 0.636 (SE 0.108) | Normal | (Vos, Corry et al. 2005) |
| Adherence to | | | |
| TCAs | 50-69% (SE 3.3%) | Uniform | (Vos, Corry et al. 2005) |
| SSRIs | 50-73% (SE 3.7%) | Uniform | (Vos, Corry et al. 2005) |

| **Parameter** | **Values** | **Uncertainty distribution** | **Source** |
|---|---|---|---|
| CBT | 50-81% (SE 4.4%) | Uniform | (Vos, Corry et al. 2005) |
| Lag to treatment | 2-6 weeks | Uniform | (Vos, Corry et al. 2005) |
| % of cases seeking care | 58.9% (RSE 2.4%) | Triangular | (Vos, Corry et al. 2005) |
| % of cases on evidence-based treatments | 59.5% of those seeking care | | (Vos, Corry et al. 2005) |
| Types of antidepressant drugs | | | |
| SSRIs | 77% (SE 0.9%) | Triangular | (Vos, Corry et al. 2005) |
| TCAs | 15% (SE 0.7%) | Triangular | (Vos, Corry et al. 2005) |
| Others | 8% (SE 0.5%) | Triangular | (Vos, Corry et al. 2005) |
| Participants group CBT | 6-8 | Uniform | (Vos, Corry et al. 2005) |
| Uncertainty fees health professionals covered by Medicare | zero | | Assumed nil |
| | | | |