

Reducing the global burden of depression

Population-level analysis of intervention cost-effectiveness in 14 world regions[†]

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Background International evidence on the cost and effects of interventions for reducing the global burden of depression remain scarce.

Aims To estimate the population-level cost-effectiveness of evidence-based depression interventions and their contribution towards reducing current burden.

Method Primary-care-based depression interventions were modelled at the level of whole populations in 14 epidemiological subregions of the world. Total population-level costs (in international dollars or I\$) and effectiveness (disability adjusted life years (DALYs) averted) were combined to form average and incremental cost-effectiveness ratios.

Results Evaluated interventions have the potential to reduce the current burden of depression by 10–30%. Pharmacotherapy with older antidepressant drugs, with or without proactive collaborative care, are currently more cost-effective strategies than those using newer antidepressants, particularly in lower-income subregions.

Conclusions Even in resource-poor regions, each DALY averted by efficient depression treatments in primary care costs less than 1 year of average per capita income, making such interventions a cost-effective use of health resources. However, current levels of burden can only be reduced significantly if there is a substantial increase in treatment coverage.

Declaration of interest None.

There is now widespread recognition of the immense burden that depression imposes on individuals, communities and health services throughout the world. Latest estimates from the Global Burden of Disease study GBD 2000 indicate that unipolar depressive disorders account for 4.4% of the global disease burden (65 million disability adjusted life years (DALYs) lost in total), in the same range as the total burden attributable to ischaemic heart disease, diarrhoeal diseases, or the combined impact of asthma and chronic obstructive pulmonary disease (World Health Organization, 2002; Üstün *et al*, 2004, this issue). What can be done to reduce this global burden, and at what cost? Although service access and treatment coverage remain low, there is growing empirical evidence from lower-income as well as higher-income countries for the effectiveness and also cost-effectiveness of a range of pharmacological and psychosocial interventions for treating and managing depression (e.g. Chisholm *et al*, 2000; Schoenbaum *et al*, 2001; Simon *et al*, 2001; Araya *et al*, 2003; Patel *et al*, 2003). Using these and other data relating to the epidemiological burden of depression, the clinical outcomes associated with different interventions and the economic costs of treatment, this analysis set out to inform mental health policy and planning through the provision of a population-level assessment of cost-effectiveness for different regions of the world.

METHOD

World Health Organization guidelines on sectoral cost-effectiveness analysis (WHO-CHOICE)

In the ongoing work programme WHO-CHOICE (CHOosing Interventions that are Cost Effective; Tan Torres *et al*, 2003),

a consistent and ‘generalised’ approach to sectoral, population-level cost-effectiveness analysis is pursued, a key feature of which is the comparison of current and new interventions for a health condition to an epidemiological scenario of no intervention. The use of such a common starting point for analysis enhances the ability to compare cost-effectiveness analysis findings across a wide range of competing interventions for reducing leading contributors to disease burden (World Health Organization, 2002). WHO-CHOICE adopts a societal perspective to the valuation of costs and effects, and is intended to identify order-of-magnitude differences in the relative cost-effectiveness of (single and combined) health strategies, with a view to reducing existing inefficiencies as well as highlighting combinations of interventions that generate most health gain for available resources.

Setting

The 192 member states of the WHO were divided into five mortality strata on the basis of their levels of child and adult mortality (World Health Organization, 2002). When these mortality strata were applied to the six regions of the WHO, they gave rise to 14 epidemiologically defined subregions (Table 1). Costs and effects of key depression interventions were modelled at the level of the total population in these subregions, and are provided in a way that allows for contextualised analyses by country-level analysts.

Population model for depression

Intervention effectiveness was determined through a state transition population model (PopMod; Lauer *et al*, 2003), which traces the development of a subregional population taking into account births, deaths and the disease in question. Susceptibles (i.e. persons not currently depressed) become cases at an instantaneous transition rate i (incidence, including recurrence); persons with a depressive episode go back to being susceptible at remission rate r ; cases are subject to the instantaneous case-fatality rate f ; and both susceptibles and cases are subject to a general mortality rate m . For all hazard rates, units are the number of events per year at risk. The model distinguishes male and female populations, each segmented into 1-year age groups. In addition, a disability weight or health state valuation is specified (on a 0–1 scale, where

[†]See pp. 386–392 and editorial, pp. 379–380, this issue.

Table 1 Prevalence of ICD-10 depressive episode (rates per 1000 population, by World Health Organization subregion)

Region and subregion	Mortality		Gender	Total population (million)	Prevalence by age group							
	Child	Adult			0-4	5-14	15-29	30-44	45-59	60-69	70-79	80+
Africa												
AfrD (e.g. Nigeria, Senegal)	High	High	Male	147.1	0.0	11.0	13.1	21.2	20.0	16.1	6.5	4.9
			Female	146.9	0.0	11.0	21.0	34.0	32.0	26.1	10.6	8.0
AfrE (e.g. Botswana, Kenya)	High	Very high	Male	171.6	0.0	11.0	13.1	21.2	20.0	16.1	6.5	4.9
			Female	173.9	0.0	11.0	21.0	34.0	32.0	26.1	10.6	8.0
The Americas												
AmrA (e.g. Canada, USA)	Very low	Very low	Male	160.5	0.0	11.0	31.0	30.1	22.3	22.0	9.6	7.8
			Female	164.7	0.0	11.0	60.2	46.5	37.8	35.3	14.3	10.9
AmrB (e.g. Brazil, Mexico)	Low	Low	Male	213.3	0.0	11.0	18.0	25.0	23.0	19.3	7.8	5.9
			Female	217.6	0.0	11.0	32.0	43.0	40.0	33.0	13.4	10.1
AmrD (e.g. Ecuador, Peru)	High	High	Male	35.5	0.0	11.0	18.0	25.0	23.0	19.3	7.8	5.9
			Female	35.8	0.0	11.0	32.0	43.0	40.0	33.0	13.4	10.1
Eastern Mediterranean												
EmrB (e.g. Iran, Saudi Arabia)	Low	Low	Male	72.2	0.0	11.0	16.0	30.0	28.0	23.0	9.0	7.1
			Female	66.9	0.0	11.0	24.0	46.0	42.0	35.3	15.3	11.7
EmrD (e.g. Egypt, Morocco)	High	High	Male	174.3	0.0	11.0	16.0	30.0	28.0	23.0	9.0	7.1
			Female	168.3	0.0	11.0	24.0	46.0	42.0	35.3	15.3	11.7
Europe												
EurA (e.g. France, Norway)	Very low	Very low	Male	201.5	0.0	11.0	19.3	19.2	17.8	14.7	6.0	4.6
			Female	210.4	0.0	11.0	41.2	44.7	39.2	34.3	14.9	10.5
EurB (e.g. Armenia, Poland)	Low	Low	Male	108.2	0.0	11.0	19.0	21.2	23.2	17.0	7.1	5.4
			Female	110.3	0.0	11.0	33.0	38.3	37.2	31.5	12.8	9.6
EurC (e.g. Estonia, Russia)	Low	Low	Male	114.1	0.0	11.0	18.0	19.5	17.8	14.0	7.0	4.5
			Female	129.1	0.0	11.4	15.4	40.0	33.9	30.0	12.8	10.0
South-East Asia												
SearB (e.g. Indonesia, Thailand)	Low	Low	Male	147.2	0.0	11.0	15.0	18.0	16.0	13.0	5.6	4.2
			Female	146.6	0.0	11.0	28.0	24.0	23.0	21.0	9.3	7.2
SearD (e.g. India, Nepal)	High	High	Male	639.1	0.0	11.0	21.0	24.0	23.0	18.4	7.5	5.7
			Female	602.7	0.0	11.0	36.0	44.7	39.2	34.3	14.9	11.4
Western Pacific												
WprA (e.g. Australia, Japan)	Very low	Very low	Male	75.8	0.0	11.0	11.0	13.6	12.0	7.8	4.0	3.0
			Female	78.6	0.0	11.0	15.0	19.6	17.0	15.0	6.0	5.0
WprB (e.g. China, Vietnam)	Low	Low	Male	785.1	0.0	11.0	18.9	19.0	24.0	18.5	7.5	5.6
			Female	747.9	0.0	11.0	15.4	28.3	47.0	36.1	15.6	12.0

Source: Global Burden of Disease study GBD 2000 documentation (<http://www.who.int/evidence/bod>).

1 equals full health) for time spent in the diseased state and also for time spent susceptible but not depressed.

The population model was run for two scenarios over a lifetime analytic horizon (100 years, by which time a 'steady state' or equilibrium has been reached), to give the total number of healthy years lived by the population. The first scenario was an epidemiological situation representing the natural history of depression (no depression interventions in place), and the second was an epidemiological situation reflecting the population-level impact of each specified

intervention (such as reduced illness duration resulting from use of an antidepressant drug), implemented for a period of 10 years (thereafter, epidemiological rates and health state valuations move back to natural history values). The difference between these two simulations represents the population-level health gain (the DALYs averted) resulting from the implementation of the intervention over a 10-year period, relative to the situation of doing nothing. In line with the GBD 2000 study, DALYs averted per year were discounted (at 3%) and age-weighted in the base case analysis.

Natural history of ICD-10 depressive episode

Depression was modelled as an episodic disorder (ICD-10 code F32, 33; World Health Organization, 1992) with a high rate of remission (recovery) and subsequent recurrence, and with excess mortality from unnatural causes (suicide). Cases of dysthymia were excluded. Comorbidity was incorporated into the epidemiological estimates underlying the population model by adopting the strategy employed in the GBD 2000 study (Üstün *et al*, 2004, this

issue); namely, only counting the case in the condition with the more severe disability (depressive episode) and subtracting that case from the prevalence figure of the other conditions (most notably, anxiety disorders and substance misuse). Using GBD 2000 disability weights for different severity levels, the composite health state valuation (HSV) for an untreated depressive episode was calculated as a weighted average of 0.62, where 1 equates to full health, giving 23% severe, HSV=0.24; 47% moderate, HSV=0.65; and 30% mild, HSV=0.86.

Point prevalence and duration for depressive episodes in different subregions were drawn from GBD 2000, based on an extensive international review of epidemiological studies (Üstün *et al*, 2004, this issue; see also Table 1). Incidence and remission rates were derived with reference to prevalence and duration as follows:

- (a) adopting the GBD 2000 estimate of 6 months (0.5 years) as the mean duration of an untreated depressive episode, an instantaneous rate of incidence can be readily calculated as double the point prevalence estimate (i.e. there is a linear relationship between incidence, prevalence and duration);
- (b) remission, by contrast, can be considered mathematically as the inverse of duration (as long as the case fatality rate is low), thereby resulting in an instantaneous (untreated) rate of remission of 2.0 (1/0.5 years).

Case fatality rates were based on a lifetime suicide risk for affective disorders of 6% among adults aged over 15 years (Inskip *et al*, 1998), with incident proportions subsequently converted into instantaneous rates. Because of a higher risk of mortality at younger ages, this rate was adjusted up to 9% for age groups between 15 and 45 years and reduced to 3% for age groups over 45 years. Consistent with a meta-analysis by Harris & Barraclough (1998), no excess risk of mortality from natural causes was attributed. Detailed tabulation of data sources and model inputs can be found for each subregion on the WHO-CHOICE website (<http://www.who.int/evidence/cea>).

Effectiveness of interventions

The expected population-level impacts of seven (self-standing or combined) primary-care-based interventions capable of being

implemented in different regions of the world were assessed:

- (a) older antidepressants: tricyclic antidepressants (TCAs, e.g. imipramine, amitriptyline);
- (b) newer antidepressants: selective serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine);
- (c) brief psychotherapy: brief cognitive therapy or problem-solving treatment;
- (d) older antidepressants plus brief psychotherapy;
- (e) newer antidepressants plus brief psychotherapy;
- (f) proactive collaborative care with older antidepressants;
- (g) proactive collaborative care with newer antidepressants.

Episodic treatment regimens for antidepressant pharmacotherapy and brief psychotherapy (interventions a–e) followed guideline-level therapeutic dosages or number of sessions over the average duration of an untreated episode. Maintenance treatment for recurrent depression was incorporated into a proactive collaborative care strategy (interventions f and g), which pursues a multifaceted disease management protocol that seeks to increase conformity with evidence-based guidelines through patient education and enhanced primary care clinician support (Katon *et al*, 2001; Simon *et al*, 2001).

The main modelled impact of intervention targeted at episodic treatment of a new depressive episode was a reduction in the duration of time depressed, equivalent to an increase in the remission rate (Table 2). Remission rates under treatment, ranging from 2.4–2.5 for psychotherapy to 2.7–2.8 for collaborative care, were based on pragmatic trials that reported the proportion of study subjects recovered at time intervals, which could be used to calculate a duration and converted into an instantaneous remission rate (Solomon *et al*, 1997; Thase *et al*, 1997; Malt *et al*, 1999; Chilvers *et al*, 2001; Katon *et al*, 2001). Brief psychotherapy was modelled to have a slightly lower rate of remission than pharmacotherapy because the onset of effect is not as rapid for more severe depression (Thase *et al*, 1997). No difference was found for combined drug and psychosocial strategies using older *v.* newer antidepressants. Following recent studies that indicate larger treatment effect sizes for both single and combined interventions

in developing countries (Araya *et al*, 2003; Bolton *et al*, 2003; Patel *et al*, 2003), a modest advantage in treated remission rates was ascribed to developing subregions. In addition, all interventions were attributed a moderate improvement in the disability level or health state valuation of an unremitted depressive episode (13–18%), resulting from increased proportions of cases moving from more to less severe health states (Table 2). Temporal symptom severity profiles for unremitted episodes were informed by a commissioned analysis of the ‘Pittsburgh 600’ data-set assembled from six research projects conducted between 1982 and 1992 (M. A. Dew, personal communication, 2001).

No intervention effect was attributed to the incidence of first episodes. However, for the estimated 56% of prevalent cases eligible for maintenance treatment (at least two lifetime episodes), the additional impact of efficacious maintenance treatment was incorporated into the proactive collaborative care strategies by reducing the incidence of recurrent episodes by 50% (i.e., an absolute risk reduction in recurrence of 0.50; Geddes *et al*, 2003). None of the selected depression interventions was credited with resulting in a reduction in case fatality, owing to the lack of robust clinical evidence that antidepressants or psychotherapy *per se* alter the relative risk of death by suicide (Storosum *et al*, 2001).

Estimates of efficacy obtained from clinical trials were adjusted to better reflect outcome in the real world, specifically with reference to treatment coverage, partial response and adherence (Table 2). Given the modest care-seeking and recognition rates observed in international studies of depression and other common mental disorders, a 50% target coverage rate was adopted for all subregions. Recent meta-analyses have reported adherence rates of 70% for TCAs and 73% for SSRIs (Barbui *et al*, 2002), and higher rates still for cognitive therapy (Gloaguen *et al*, 1998), but these can be viewed as upper limits given the controlled research environment within which source studies were conducted. Accordingly, these adherence rates were adjusted downwards by a further ‘real world’ factor of 0.6–0.75 to give an overall level of adherence of between 45% and 55%.

Costs of interventions

Costs were considered at the patient level and the programme level. Programme-level

Table 2 Changes to model parameters as a result of intervention effects

Model scenario	Parameter ¹	Estimate (efficacy) ²	% Improvement (efficacy) ³	Coverage	Adherence	Partial response ⁴	Estimate (effectiveness) ²	% Improvement (effectiveness) ³
0 Null (no intervention)	Health state valuation	0.62						
	Remission hazard rate	2.00						
	Incidence hazard rate ⁵	2 × prevalence						
(a) Pharmacotherapy: TCAs	Health state valuation	0.70	12.9	50%	60%	20%	0.65	4.5
	Remission hazard rate	2.6–2.7	30–35				2.17–2.21	9.0–10.5
(b) Pharmacotherapy: SSRIs	Health state valuation	0.705	13.7	50%	63%	20%	0.65	5.0
	Remission hazard rate	2.6–2.7	30–35				2.18–2.22	9.5–11.0
(c) Psychotherapy	Health state valuation	0.71	14.5	50%	70%	20%	0.66	5.8
	Remission hazard rate	2.4–2.5	20–25				2.14–2.18	7.0–8.8
(d) TCA+psychotherapy	Health state valuation	0.72	16.1	50%	70%	15%	0.66	6.3
	Remission hazard rate	2.6–2.7	30–35				2.21–2.25	10.5–12.3
(e) SSRI+psychotherapy	Health state valuation	0.72	16.1	50%	70%	15%	0.66	6.3
	Remission hazard rate	2.6–2.7	30–35				2.21–2.25	10.5–12.3
(f) TCA+proactive care	Health state valuation	0.73	17.7				0.67	7.3
	Remission hazard rate	2.7–2.8	35–40	50%	75%	15%	2.26–2.30	13.1–15.0
	Incidence hazard rate ⁵	$Inc_{null} \times 56\% \times 50\%$	28.0					8.9
(g) SSRI+proactive care	Health state valuation	0.73	17.7				0.67	7.3
	Remission hazard rate	2.7–2.8	35–40	50%	75%	15%	2.26–2.30	13.1–15.0
	Incidence hazard rate ⁵	$Inc_{null} \times 56\% \times 50\%$	28.0					8.9

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

1. Parameter changed for period of intervention implementation (10 years) among treated population over 14 years old.

2. Lower-range values relate to developed subregions; higher-range values relate to developing subregions (see text for sources).

3. Percentage improvement relative to the null scenario of no intervention.

4. Percentage of those treated who do not adhere fully but do get some treatment response (50% of the change in health state valuation of those who fully adhere).

5. Null incidence rate, Inc_{null} , equals double the prevalence rate (see text). Under proactive care, the 56% of episodes which are recurrent are reduced by 50%.

costs included central administration and training, with an estimate of 2–3 days per trainee used for training primary care doctors and case managers in the management of depression, whereas 10 days of initial training (including role play) and 2 days of supervision per year were allocated for psychosocial treatments (Dowrick *et al*, 1998). Patient-level resource use profiles per 6-month treatment period were generated for each severity category of depressive episode, based on data from prospective studies (Chisholm *et al*, 2000; Katon *et al*, 2001; Simon *et al*, 2001; Patel *et al*, 2003) and also informed by a dedicated multi-country Delphi consensus study of resource use in developing countries (Ferri *et al*, 2004). Resource use components included, as applicable, drug dosage and frequency (e.g. 20 mg fluoxetine daily); brief psychotherapy (6–8 sessions); case management (4–6 contacts); primary care (3–6 visits); psychiatric out-patient care (33–66% of cases, 4–6 visits); and in-patient

stays (5–15% of moderate–severe cases, 1–2 weeks). The severity-weighted estimate for each resource component was then multiplied by the subregion-specific unit cost of the service, to give a mean cost per treated episode.

Unit costs of primary and secondary care services were derived from an econometric analysis of a multinational data-set of hospital costs, using gross national income per capita (plus other explanatory variables) to predict unit costs in different WHO subregions (Adam *et al*, 2003). For the costs of antidepressant medication, supplier prices for generically produced drugs (e.g. \$0.01 per 25 mg amitriptyline or imipramine tablet, equivalent to \$0.03–0.05 per daily dose) were obtained from the International Drug Price Indicator Guide for the year 2000 (<http://erc.msh.org/dmpguide>), with deviations from the baseline price for SSRIs assessed by sensitivity analysis (e.g. unit prices of \$0.10 and \$1.00 per 20 mg fluoxetine were considered

alongside a baseline value of \$0.25, reflecting expected variations in both the extent of government bulk purchasing for primary care providers and also the availability of generic, rather than branded, products).

Mean costs per episode were multiplied by the number of treated episodes in the subregional population (at a coverage rate of 50%), to give a total cost of care for 1 year of implementation. Fully worked resource profiles and cost templates for all interventions in each subregion can be found on the WHO-CHOICE website (<http://www.who.int/evidence/cea/region/region>). All baseline analysis costs for the 10-year implementation period were discounted at 3% and expressed in international dollars (I\$), which adjust for differences in the relative price and purchasing power of countries and thereby facilitate interregional analysis. That is, I\$1 buys the same quantity of health care resources in China or India as it does in the USA.

Uncertainty analyses

First, a series of one-way sensitivity analyses that assessed the impact on final cost-effectiveness analysis results of discounting and age-weighting were performed. Second, best- and worst-case scenarios incorporating upper and lower values for key drivers of cost (unit price of SSRI drugs and health care services, the proportion of individuals using secondary services) and treatment effectiveness (efficacy and adherence) were generated. Third, baseline data (with pessimistic and optimistic scenarios as lower and upper ranges) were entered into an analytical software package (MCLeague; Tan Torres *et al*, 2003), which performs a probabilistic uncertainty analysis using Monte Carlo simulation (2000 runs were made, using a truncated normal distribution).

RESULTS

Intervention effectiveness and averted burden of depression

Total population effects of different depression interventions are reported in Table 3. Proactive collaborative care strategies had the greatest impact on population health (close to double the number of DALYs averted by antidepressants or psychotherapy alone), on account of the additional benefits that come from avoiding a significant proportion of recurrent depressive episodes. Total population-level health gains can be expressed as a proportion of GBD 2000 depression burden for each subregion, which shows that, at a treatment coverage level of 50%, antidepressants and brief psychotherapy on their own (interventions a–c) could avert between 9% and 15% of the current burden, whereas combination strategies d and e could avert 11–18% and the proactive collaborative care strategies could avert 18–29% of DALYs attributed to depression. The health gain per treated episode, similar in concept to the ‘depression-free day’ (Simon *et al*, 2001), is also shown in Table 3, and demonstrates that single interventions (a–c) achieve between 18 and 23 disability-free or healthy days per treated episode, combined interventions (d and e) 23–28 days and proactive collaborative care strategies (f and g) 24–29 days. Although proactive care generates much greater total gain in the population, its individual effect is not appreciably different on

account of the larger number of individuals receiving treatment.

Costs and cost-effectiveness of interventions

Patient-level costs per treated episode are shown in Table 4. As expected, there is considerable variation in the average cost of a treated episode, both between subregions and also between interventions. The lowest patient-level costs per treated episode relate to older antidepressants, ranging from I\$50–80 in high-mortality developing subregions (AfrD, AfrE, AmrD, EmrD, SearD) to approximately I\$400 in the most economically developed subregions (AmrA, EurA, WprA). At the other end of the cost spectrum, the average cost per treated episode for proactive collaborative care with newer generic antidepressants (intervention g) ranges from I\$130–150 in high-mortality developing regions to I\$700–750 in developed subregions. Programme-level costs accounted for only 1–10% of total costs, with the highest proportion applicable to brief psychotherapy because of more intensive training needs. Total intervention costs per year for each subregion are reported in Table 4, which illustrates further the wide variation in costs, as a function of both differential price levels and population size. The differential cost of care between pharmacological interventions with TCAs *v.* SSRIs is greater in lower-income regions than in industrialised subregions, a consequence of the relatively high price payable in low-income subregions for newer antidepressant drugs (to illustrate, one newer antidepressant tablet bought at a price of \$1 would be equivalent to 25% of the cost of an outpatient visit in African subregions, compared with 2% in North America).

Relative to the natural history of depression, and before allowance for model uncertainty, the most cost-effective stand-alone intervention in all subregions was pharmacotherapy with older antidepressants (cost per DALY averted: I\$700–1000 in high-mortality developing subregions AfrD, AfrE, AmrD, EmrD, SearD; I\$1100–1800 in low-mortality developing regions AmrB, EmrB, SearB, WprB; and I\$1600–1700 in developed subregions AmrA, EurA, EurB, EurC, WprA). Across the 14 subregions, newer antidepressants had an average cost-effectiveness ratio (CER) in the range I\$1000–7000, which resulted in an

incremental CER of I\$7500–9000 for moving from older to newer antidepressants (Table 4). The incremental CER for psychotherapy alone *v.* older antidepressants was more variable (reflecting differences in psychotherapists’ salaries), ranging from I\$6000–7000 in high-mortality developing subregions to nearly I\$50 000 in developed subregions with very low rates of child and adult mortality. The most cost-effective combination strategy was proactive collaborative care with older antidepressants (incremental CER: I\$1650–1850 in high-mortality developing subregions; I\$2000–3000 in low-mortality developing subregions; I\$2300–14 000 in developed subregions). In all subregions, the incremental CER of pharmacotherapy with older antidepressants – and with the exception of the lowest-income subregions, proactive collaborative care with older antidepressants too – was considerably less than average yearly income per capita, which is an international threshold value recently proposed for accepting an intervention as very cost-effective (Commission on Macroeconomics and Health, 2001).

Uncertainty analysis

Summary findings of a series of one- and multi-way sensitivity analyses are presented in Table 5. Substitution of the baseline discount rate of 3% with values of 0% and 6% altered total costs and average CERs for all interventions by 14% and –11%, respectively. The removal of age-weighting had a more significant impact on results, reducing total health gain estimates by 16–25% across subregions (resulting in a corresponding increase of 19–34% in average CERs). Under the best-case scenario (see Table 5 for details), total costs were 30–50% lower and total effects 24–30% higher than base case results, thereby lowering the average cost per DALY averted by 50–60%. Results for the worst-case scenario were more extreme, with respective increases of 45–90% and 110–220% in the average cost and cost-effectiveness of interventions using older antidepressant drugs, and even larger changes for interventions with newer antidepressants because of the significantly higher drug price. To illustrate, the average CER for pharmacotherapy with SSRIs in the Western Pacific subregion WprB baseline value: I\$1560) ranged from I\$600 to I\$7000. Under the best-case scenario, the rank order of cost-effectiveness was

Table 3 Population-level intervention effectiveness and averted burden of depression by World Health Organization subregion

	Africa			The Americas				Eastern Mediterranean			Europe			South-East Asia		Western Pacific	
	AfrD	AfrE	AfrA	AmrB	AmrA	AmrB	AmrD	EmrB	EmrD	EurA	EurB	EurC	SearB	SearD	WprA	WprB	
Total population (million)	294.1	345.5	325.2	430.9	71.2	139.1	342.6	411.9	218.5	243.2	293.8	1241.8	154.4	1532.9			
Current burden of depression (DALYs, 000) ¹	1906	2154	5031	5589	867	1184	3507	4074	2548	2634	2832	17 123	1000	14 515			
Total population effect (DALYs averted per year)²																	
(a) Older antidepressants: TCAs	243 409	268 381	503 869	564 188	87 249	173 568	406 517	503 574	260 119	239 342	257 055	1 619 708	95 459	1 759 925			
(b) Newer antidepressants: SSRIs	256 912	283 377	534 199	595 157	92 059	183 250	429 377	533 238	275 660	253 735	271 535	1 709 838	101 234	1 859 678			
(c) Brief psychotherapy	253 865	280 251	541 470	588 449	90 988	181 017	424 114	540 939	279 301	257 301	267 825	1 689 800	102 297	1 835 781			
(d) TCA+psychotherapy	302 856	334 118	635 069	702 036	108 562	215 975	505 921	634 539	327 713	301 648	319 642	2 015 752	120 155	2 189 831			
(e) SSRI+psychotherapy	302 856	334 118	635 069	702 036	108 562	215 975	505 921	634 539	327 713	301 648	319 642	2 015 752	120 155	2 189 831			
(f) TCA+proactive care	477 102	525 494	1 031 234	1 105 894	171 151	340 530	797 291	1 029 952	532 555	489 201	502 500	3 175 356	195 202	3 447 334			
(g) SSRI+proactive care	477 102	525 494	1 031 234	1 105 894	171 151	340 530	797 291	1 029 952	532 555	489 201	502 500	3 175 356	195 202	3 447 334			
% current burden of depression averted																	
(a) Older antidepressants: TCAs	12.8%	12.5%	10.0%	10.1%	10.1%	14.7%	11.6%	12.4%	10.2%	9.1%	9.1%	9.5%	9.5%	12.1%			
(b) Newer antidepressants: SSRIs	13.5%	13.2%	10.6%	10.6%	10.6%	15.5%	12.2%	13.1%	10.8%	9.6%	9.6%	10.0%	10.1%	12.8%			
(c) Brief psychotherapy	13.3%	13.0%	10.8%	10.5%	10.5%	15.3%	12.1%	13.3%	11.0%	9.8%	9.5%	9.9%	10.2%	12.6%			
(d) TCA+psychotherapy	15.9%	15.5%	12.6%	12.6%	12.5%	18.2%	14.4%	15.6%	12.9%	11.5%	11.3%	11.8%	12.0%	15.1%			
(e) SSRI+psychotherapy	15.9%	15.5%	12.6%	12.6%	12.5%	18.2%	14.4%	15.6%	12.9%	11.5%	11.3%	11.8%	12.0%	15.1%			
(f) TCA+proactive care	25.0%	24.4%	20.5%	19.8%	19.7%	28.8%	22.7%	25.3%	20.9%	18.6%	17.7%	18.5%	19.5%	23.8%			
(g) SSRI+proactive care	25.0%	24.4%	20.5%	19.8%	19.7%	28.8%	22.7%	25.3%	20.9%	18.6%	17.7%	18.5%	19.5%	23.8%			
Health gain per treated episode ('disability-free days')³																	
(a) Older antidepressants: TCAs	21.0	20.0	18.5	20.6	21.8	22.1	21.3	18.5	18.9	18.0	19.8	20.9	19.2	21.3			
(b) Newer antidepressants: SSRIs	22.3	21.2	19.7	21.9	23.1	23.5	22.6	19.7	20.1	19.2	21.0	22.2	20.4	22.6			
(c) Brief psychotherapy	22.1	21.1	20.2	21.7	23.0	23.3	22.4	20.1	20.6	19.6	20.8	22.0	20.8	22.5			
(d) TCA+psychotherapy	26.3	25.0	23.4	25.8	27.2	27.7	26.6	23.4	23.9	22.7	24.7	26.1	24.2	26.6			
(e) SSRI+psychotherapy	26.3	25.0	23.4	25.8	27.2	27.7	26.6	23.4	23.9	22.7	24.7	26.1	24.2	26.6			
(f) TCA+proactive care	27.1	25.9	24.9	26.6	28.2	28.6	27.5	24.9	25.4	24.2	25.5	27.0	25.8	27.5			
(g) SSRI+proactive care	27.1	25.9	24.9	26.6	28.2	28.6	27.5	24.9	25.4	24.2	25.5	27.0	25.8	27.5			

DALY, disability-adjusted life-year; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
 1. Total discounted, age-weighted DALYs attributable to unipolar major depression for year 2000 (WHO, 2001).
 2. Total discounted, age-weighted DALYs averted by intervention per year, relative to no intervention (50% treatment coverage).
 3. Undiscounted, non-age-weighted DALYs averted, converted into days and divided by total number of treated episodes.

Table 4 Population-level costs and cost-effectiveness of depression interventions by World Health Organization subregion (costs shown in international dollars (\$) at 2000 rates)

	Africa		The Americas			Eastern Mediterranean			Europe			South-East Asia		Western Pacific	
	AfrD	AfrE	AmrA	AmrB	AmrD	EmrB	EmrD	EurA	EurB	EurC	SearB	SearD	WprA	WprB	
Gross national income per capita (\$)	1381	1576	31477	7833	3837	7870	2393	23927	5873	6916	3915	1449	27534	4186	
Patient-level cost per episode (\$) ¹															
(a) Older antidepressants: TCAs	54	55	459	135	82	87	63	391	103	117	83	53	424	86	
(b) Newer antidepressants: SSRIs	88	88	493	169	116	121	97	425	137	151	117	87	458	120	
(c) Brief psychotherapy	75	75	697	173	101	112	79	611	126	141	102	73	653	106	
(d) TCA+psychotherapy	93	93	772	196	119	132	96	682	145	160	120	90	726	124	
(e) SSRI+psychotherapy	130	130	809	234	156	169	133	719	182	197	157	128	763	161	
(f) TCA+proactive care	92	92	731	176	108	122	89	656	128	140	109	88	693	112	
(g) SSRI+proactive care	132	132	772	217	148	162	130	696	168	180	149	129	733	152	
Total population cost (\$m per year) ²															
(a) Older antidepressants: TCAs	178	214	3555	1018	90	192	336	3207	409	469	300	1133	652	2092	
(b) Newer antidepressants: SSRIs	284	337	3816	1271	127	264	513	3480	542	603	421	1844	702	2903	
(c) Brief psychotherapy	253	299	5385	1307	111	249	442	4958	516	562	382	1539	988	2645	
(d) TCA+psychotherapy	311	364	5977	1480	131	291	527	5555	586	643	445	1915	1106	3072	
(e) SSRI+psychotherapy	428	501	6269	1760	172	372	724	5862	734	791	580	2697	1164	3975	
(f) TCA+proactive care	594	687	11278	2642	236	529	968	10596	1028	1111	799	3721	2080	5480	
(g) SSRI+proactive care	843	977	11896	3241	323	700	1386	11244	1341	1428	1088	5406	2199	7402	
Average CER (\$ per DALY) ³															
(a) Older antidepressants: TCAs	733	799	7055	1805	1034	1108	827	6368	1574	1960	1165	700	6828	1189	
(b) Newer antidepressants: SSRIs	1105	1188	7143	2136	1379	1443	1194	6526	1966	2376	1551	1078	6936	1561	
(c) Brief psychotherapy	998	1067	9946	2220	1223	1378	1043	9165	1846	2186	1428	911	9661	1441	
(d) TCA+psychotherapy	1026	1089	9411	2109	1208	1350	1042	8754	1789	2131	1392	950	9204	1403	
(e) SSRI+psychotherapy	1414	1498	9871	2507	1582	1721	1432	9238	2240	2623	1816	1338	9687	1815	
(f) TCA+proactive care	1244	1307	10936	2389	1377	1553	1214	10288	1929	2272	1590	1172	10653	1590	
(g) SSRI+proactive care	1767	1858	11536	2931	1886	2056	1738	10917	2519	2920	2164	1702	11264	2147	
ICER (\$ per DALY) ⁴															
Older antidepressants=lowest CER	733	799	7055	1805	1034	1108	827	6368	1574	1960	1165	700	6828	1189	
SSRIs v. TCAs (b v. a)	7800	8152	8607	8165	7643	7461	7727	9216	8524	9299	8408	7888	8719	8135	
Psychotherapy v. TCAs (c v. a)	7159	7145	48690	11885	5623	7670	6028	46861	5536	5199	7690	5787	49209	7289	
TCA+psychotherapy v. TCA only (d v. a)	2224	2276	18462	3353	1919	2339	1924	17931	2616	2789	2324	1974	18385	2279	
SSRI+psychotherapy v. TCAs only (e v. a)	4202	4354	20690	5382	3825	4231	3905	20275	4804	5172	4489	3950	20736	4380	
Proactive care+TCAs v. TCAs only (f v. a)	1777	1838	14644	2998	1734	2017	1616	14038	2269	2571	2036	1664	14314	2008	
Proactive care+SSRIs v. TCAs only (g v. a)	2845	2965	15817	4104	2772	3042	2687	15268	3421	3839	3211	2746	15509	3147	

ICER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

1. Discounted patient-level treatment costs per 6-month episode.

2. Total discounted programme and patient-level cost per year (50% treatment coverage in population).

3. Average CER=total population-level intervention cost per year/total DALYs averted by intervention per year.

4. ICER values in **bold** are most cost-effective single and combined interventions.

Table 5 One-way and multi-way sensitivity analyses by World Health Organization subregions

Sensitivity analysis	Parameter	Africa		The Americas			Eastern Mediterranean		Europe		South-East Asia		Western Pacific		
		AfrD %	AfrE %	AmrA %	AmrB %	AmrD %	EmrB %	EmrD %	EurA %	EurB %	EurC %	SearB %	SearD %	WprA %	WprB %
1 Costs not discounted	Total cost	13	13	14	14	14	13	13	14	14	14	14	14	13	14
	Average CER	13	13	14	14	14	13	13	14	14	14	14	14	13	14
2 Costs discounted at 6%	Total cost	-10	-10	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11
	Average CER	-10	-10	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11
3 Effects not age-weighted (but discounted at 3%)	Total effect	-25	-25	-21	-23	-25	-24	-24	-18	-21	-18	-24	-24	-16	-19
	Average CER	34	34	26	30	33	31	31	21	26	21	31	32	19	23
4 Effects not age-weighted or discounted	Total effect	-8	-9	-2	-5	-6	-5	-6	2	-3	0	-6	-6	3	0
	Average CER	8	9	2	5	7	5	6	-1	3	0	6	7	-3	0
5 Best-case scenario ¹															
(a) Older antidepressants: TCAs	Average CER	-46	-47	-51	-54	-54	-51	-52	-50	-55	-55	-54	-46	-50	-54
(b) Newer antidepressants: SSRIs	Average CER	-59	-59	-53	-59	-62	-59	-62	-52	-61	-61	-62	-61	-52	-61
(c) Brief psychotherapy	Average CER	-53	-53	-56	-58	-58	-56	-55	-55	-57	-59	-57	-76	-55	-57
(d) TCA+psychotherapy	Average CER	-48	-48	-53	-54	-53	-51	-51	-52	-53	-54	-53	-66	-52	-53
(e) SSRI+psychotherapy	Average CER	-57	-57	-54	-58	-60	-58	-59	-53	-59	-59	-59	-69	-53	-59
(f) TCA+proactive care	Average CER	-45	-45	-48	-50	-49	-48	-47	-48	-49	-50	-49	-69	-48	-49
(g) SSRI+proactive care	Average CER	-56	-56	-50	-56	-58	-56	-58	-50	-57	-57	-57	-74	-50	-57
6 Worst-case scenario ²															
(a) Older antidepressants: TCAs	Average CER	166	173	210	223	215	203	201	199	227	231	217	176	203	217
(b) Newer antidepressants: SSRIs	Average CER	359	358	243	315	351	335	367	238	339	331	352	372	237	348
(c) Brief psychotherapy	Average CER	169	174	195	219	218	203	199	186	224	234	215	181	189	216
(d) TCA+psychotherapy	Average CER	137	141	165	184	178	167	162	157	188	195	177	145	160	179
(e) SSRI+psychotherapy	Average CER	286	288	189	264	299	279	304	185	287	287	295	303	185	293
(f) TCA+proactive care	Average CER	111	114	132	145	140	133	128	127	147	153	139	116	129	140
(g) SSRI+proactive care	Average CER	257	259	157	230	265	248	272	154	254	253	262	268	155	261

CER, cost-effectiveness ratio; SSRI, specific serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Notes (changes in parameter values relative to base case):

1. Costs: lower price of SSRI (US\$0.10); lower 95% CI for unit costs of health care services; 50% lower rate of in-patient admission/out-patient attendance. Effects: 10% increase in treatment efficacy (remission/reduced duration) and adherence.
2. Costs: higher price of SSRI (US\$1.00); upper 95% CI for unit costs of health care services; 50% higher rate of in-patient admission/out-patient attendance. Effects: 10% decrease in treatment efficacy (remission/reduced duration) and adherence.

unchanged in all but the three high-income subregions (AmrA, EurA and WprA, where generic SSRIs become the most cost-effective strategy); under the worst-case scenario, the combined approach of TCAs plus proactive care became the single most cost-effective strategy in Eastern Europe (subregions EurB and EurC), but elsewhere the rank order was preserved.

Finally, by entering costs and effectiveness data into a stochastic uncertainty framework, it is possible to assess the likelihood of each intervention being considered cost-effective at different levels of resource availability. Figure 1 provides a graphical display of these competing probabilities in the South-East Asian subregion SearD. In this subregion, pharmacotherapy with older antidepressants is the cost-effective choice when resources are very restricted (other interventions exceed the available budget), but at higher resource levels the probability is reduced as other single or combined interventions, including psychotherapy and proactive collaborative care, become candidates for inclusion (for example, proactive collaborative care with older antidepressants becomes most likely to be cost-effective once the level of resource availability is quadrupled). Similar in concept to cost-effectiveness acceptability curves, this approach to uncertainty analysis provides decision-makers with information on the most economically feasible strategies for reducing the current burden of depression over the short- and

longer-term, while acknowledging the inherent imprecision underlying baseline results.

DISCUSSION

In light of the increasing international public health attention to the burden of depression, this study set out to examine the population-level cost-effectiveness of key health care strategies capable of reducing this burden in different subregions of the world. The purpose of such an exercise is to locate the broad, relative position of effective and applicable depression interventions within a wider cost-effectiveness and priority-setting framework in the health care sector.

Depression care and health sector efficiency

Using the criteria of the Commission for Macroeconomics and Health (2001), the results of this study indicate that implementation of efficient depression interventions in primary care settings would be very cost-effective (each DALY averted costs less than 1 year of average per capita income). These findings therefore provide relevant new information to health policy makers regarding the relatively good value of investing in depression treatment, and in so doing could help to remove one of many remaining barriers to a more appropriate public health response to the burden of common mental disorders.

Comparison of results with other cost-effectiveness analysis studies of depression that have employed population-level approaches to health measurement is limited, although one study of a quality improvement programme from North America (Schoenbaum *et al*, 2001) reported an incremental cost per quality-adjusted life year of \$9500–36 000 for medication and psychotherapy regimens over usual primary care, which is in the same range as that given here for subregion AmrA. Estimated 'depression-free days' (18–28 additional days per 6-month treatment period compared with no treatment) were also in line with other studies that have used this metric. Simon *et al* (2001), for example, report an incremental gain of 12.6–16.7 depression-free days for collaborative care over usual primary care. When considered alongside the cost-effectiveness of other interventions evaluated by WHO-CHOICE to date, interventions for depression are in the same range as treatment strategies for reducing hypertension or cholesterol levels (World Health Organization, 2002), suggesting that evidence-based interventions for depression could have just as much a claim on scarce health resources as those for other chronic, non-communicable conditions that impose a significant burden on societies.

Reducing the global burden of depression

In terms of global effectiveness, evaluated interventions can potentially avert between 7 and 14 (out of 65) million DALYs, yet by expressing these health gains as a proportion of the current (and very largely untreated) burden of depression – ranging from 10% to 30% – it is evident that these technologies have a limited impact at the population level, even at a target coverage rate in excess of that prevailing now in most regions. A similar finding was reached in a recent analysis for Australia, where an estimated 22% of the burden of depression is currently being averted by specific treatment, and only 45% of the current burden would be avoided even at a 100% effective coverage rate (Andrews *et al*, 2000). Over and above health system challenges such as increased access or coverage, there is therefore an evident need to increase the capability or efficacy of pharmacological and psychosocial treatments to resolve depressive symptoms promptly, as well as to avert their occurrence or recurrence

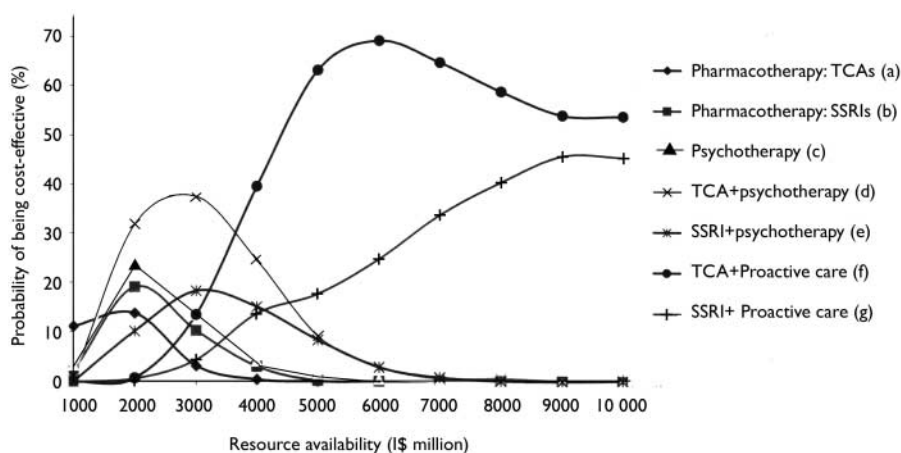


Fig. 1 Probabilistic uncertainty analysis of depression interventions for South-East Asian subregion SearD. I\$, international dollars.

through the development of effective community-based prevention and promotion strategies.

Interregional variation in the cost-effectiveness of interventions

A central debate in the health economics of depression concerns whether the higher acquisition costs of newer antidepressants are offset by greater compliance and reductions in use of health care and other services (Barbui *et al*, 2002). The results from this analysis, in which a small advantage for SSRIs in terms of adherence and disability improvement was modelled, suggest that a cost-offset hypothesis currently has limited pertinence in low-income subregions, since the higher acquisition price of generic SSRIs increases total costs of care substantially (if branded newer antidepressants were used, the costs would be far higher still). Consequently, the baseline incremental CER of I\$7500–9000 for moving from older to newer antidepressants constitutes a relatively cost-ineffective use of resources in resource-poor subregions, whereas in the most industrialised subregions such a ratio could easily be justified on efficiency grounds. However, and as examined in the best-case scenario analysis, this situation can be expected to change as the price of generic SSRIs falls, as it has already done in countries such as India (the incremental CER for all subregions falls below I\$2000).

By contrast, and notwithstanding the severe current shortage of training, lower salaries make the use of brief evidence-based psychotherapy a potentially more attractive treatment alternative to older antidepressants in developing regions compared with high-income regions. Finally, there appear to be good grounds for thinking that proactive care strategies incorporating maintenance treatment offer a cost-effective option in all regions, as a significant reduction in the incidence of recurrent episodes (plus increased adherence) is achieved at a moderate additional cost (follow-up by a case manager).

Limitations of the population-based modelling approach

This analysis is constrained in a number of important respects. First, the use of epidemiological subregions as the unit of analysis is a compromise between a global level of aggregation and country-by-country assessment. Because policies are implemented

by individual countries, there is a clear requirement to contextualise subregional estimates down to this level, in particular adjusting results for local variations in epidemiology, clinical effectiveness, service use patterns and unit costs. Such a process is now well under way in a number of countries as part of the WHO-CHOICE programme, results from which will provide an important test of the validity of the models used here. Second, the analysis did not confront the complex issue of comorbidity in depression, other than by including individuals for whom the co-occurring illness had a lower level of disability than the depression (e.g. anxiety disorders). Because treatment response might be slower in comorbid cases, as well as more costly to obtain, this is a potential source of overestimation of effectiveness and cost-effectiveness, which future revisions might be able to correct for as more knowledge on the costs and effects of treatments for comorbid depression becomes available.

Third, the population and costing models rest upon a series of best estimates, including the average duration of depressive episodes (plus related GBD 2000 parameters), expected patterns of resource use and, perhaps most importantly, estimates of intervention efficacy. Efficacy estimates were drawn mainly from trials undertaken in industrialised countries, although recent controlled trials from India, Uganda and Chile found treatment effects at least as large as studies carried out in the USA and UK for antidepressant therapy, group psychotherapy and proactive care respectively (Araya *et al*, 2003; Bolton *et al*, 2003; Patel *et al*, 2003). Uncertainty analyses can help in assessing the sensitivity and robustness of baseline estimates, and showed that whereas absolute values could deviate from base case findings by as much as half or more than double, the prevailing pattern or rank order of intervention cost-effectiveness was preserved in all low- and middle-income subregions. However, there clearly remain important questions around, for example, the transferability and cultural sensitivity of structured psychotherapies to regions as diverse as Africa, Asia and Latin America.

Finally, and despite the pursuit of a societal perspective, considerable challenges in the international measurement of productivity gains and of patient and informal carer time spent seeking or providing care have precluded their valuation in the present analysis (Tan

Torres *et al*, 2003). Incorporation of these wider costs and consequences, however, would be expected only to enhance the cost-effectiveness of depression interventions (Chisholm *et al*, 2000; Patel *et al*, 2003).

From economic evidence to mental health service development

Evidence for the comparative cost-effectiveness of interventions for depression provides only one input into the decision-making process. Mental health policy makers also need to address a series of issues beyond which interventions to choose purely from an efficiency perspective, most notably how to increase access to services of sufficient quality to ensure both the continuity of and adherence to these effective treatments. Moving from today's very modest level of effective treatment coverage to one that can make a significant impression on the existing burden of depression will require political commitment, public awareness campaigns and investment in health professionals working in primary and mental health care.

ACKNOWLEDGEMENTS

The work was supported under WHO's Global Programme on Evidence for Health Policy. The work of J.L.A.-M. was supported by the Spanish Fondo de Investigacion Sanitaria (Contract No. 02/10069). We warmly acknowledge the following colleagues, who have actively contributed to the conceptual and methodological development of WHO-CHOICE: Taghreed Adam, Rob Baltussen, David Evans, Raymond Hutubessy, Ben Johns, Jeremy Lauer, Christopher Murray and Tessa Tan Torres. We also thank Gavin Andrews, Theo Vos and Mark van Ommeren for comments on an earlier version of this paper. The views expressed are those of the authors and not necessarily those of the organisations they represent.

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CLINICAL IMPLICATIONS

- Primary-care-based depression interventions have the potential to reduce the current burden of depression by 10–30%.
 - Proactive care strategies incorporating maintenance treatment for recurrent depression yield considerably greater population-level health gain than episodic treatments.
 - On efficiency grounds alone, interventions using older antidepressants are currently more cost-effective than those using newer antidepressants, particularly in lower-income regions.
- ## LIMITATIONS
- Estimates of depression treatment efficacy, mainly from industrialised countries, have been generalised to world regions without a robust empirical evidence base.
 - Analysis was performed at the highly aggregated level of world subregions, whereas resource allocation decisions are ultimately made at the level of individual countries.
 - The wider economic consequences of depression and its treatment, including lost work opportunities, were not measured.

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(First received 18 July 2003, final revision 2 December 2003, accepted 15 December 2003)

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