Costs and consequences of enhanced primary care for depression

Systematic review of randomised economic evaluations

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Background A number of enhancement strategies have been proposed to improve the quality and outcome of care for depression in primary care settings. Decision-makers are likely to need to know whether these interventions are cost-effective in routine primary care settings.

Method We conducted a systematic review of all full economic evaluations (cost-effectiveness and cost–utility analyses) accompanying randomised controlled trials of enhanced primary care for depression. Costs were standardised to UK pounds/US dollars and incremental cost-effectiveness ratios (ICERs) were visually summarised using a permutation matrix.

Results We identified 11 full economic evaluations (4757 patients). A near-uniform finding was that the interventions based upon collaborative care/case management resulted in improved outcomes but were also associated with greater costs. When considering primary care depression treatment costs alone, ICER estimates ranged from £7 ($13, no confidence interval given) to £13 ($24, 95% CI −105 to 148) per additional depression-free day. Educational interventions alone were associated with increased cost and no clinical benefit.

Conclusions Improved outcomes through depression management programmes using a collaborative care/case management approach can be expected, but are associated with increased cost and will require investment.

Declaration of interest None.

A number of organisational and educational strategies have been proposed to improve the recognition and management of depression in primary care (Gilbody *et al*, 2003; Bower & Gilbody, 2005). These include educative strategies targeted at primary care physicians; clinical practice guidelines and a range of strategies to implement them (Cabana *et al*, 2002); and collaborative care, involving an enhanced case management role for non-medical specialists such as practice nurses and integrated working relationships between primary care and specialist/secondary services (Katon *et al*, 2001*b*).

In the UK, educational interventions based upon consensus guidelines have formed the cornerstone of quality improvement strategies, such as the Defeat Depression Campaign (Paykel & Priest, 1992). More recently more intensive organisational strategies such as case management and stepped care have been cautiously recommended by the National Institute for Clinical Excellence (2004). In addition, there are specific governmental initiatives to encourage primary care physicians to provide 'enhanced care' for depression (National Institute for Mental Health in England, 2004), with economic incentives attached.

Decision-makers increasingly seek information on both clinical effectiveness and cost-effectiveness, in order to make optimal decisions about the use of limited healthcare resources (NHS Centre for Reviews and Dissemination, 2001*a*). Systematic reviews of randomised controlled trials are considered the highest quality source of research evidence, but this method of data synthesis has not hitherto been applied to economic data in this area of practice and policy. We therefore conducted a systematic review of economic evaluations of methods of organising and delivering enhanced primary healthcare for depression.

METHOD

We conducted a systematic review of economic studies according to accepted guidelines (NHS Centre for Reviews and Dissemination, 2001*b*), and specifically used a method proposed by Nixon *et al* (2001) to summarise data from individual economic evaluations where meta-analysis cannot routinely be applied.

Inclusion criteria

Economic studies were selected that examined the cost-effectiveness of organisational interventions to improve the quality and outcome or care for depression in primary care settings. These organisational interventions could include:

(a) clinician education;

(b) dissemination and implementation of treatment or management guidelines;

(c) reconfiguration of roles within primary care;

(d) case management or active follow-up;

(e) consultation–liaison or other methods of improving working relationships between primary care and specialist/secondary services.

Studies that specifically examined the effectiveness of psychotherapy or drug treatments alone (e.g. Lave *et al*, 1998) were not included, although many of the enhancements outlined above included these as components of care. We sought all full economic evaluations (cost–benefit analyses, cost-effectiveness analyses, cost-minimisation analyses or cost–utility analyses) based upon robust randomised epidemiological designs (Gold *et al*, 1996; Drummond *et al*, 1997) – see the Appendix for definitions and examples of these terms.

Search strategies

We searched the following databases from inception to November 2005: Medline, EMBASE, CINAHL, PsycLIT, EconLIT, the Cochrane Library, the NHS Economic Evaluations Database, the Health Economic Evaluations Database and the Database of Abstracts of Reviews of Effectiveness. Search strategies included search terms relating to depression; primary care and quality improvement strategies, developed from strategies used within the Cochrane Effective Practice and Organisation of Care group (Bero *et al*, 1998) and optimal search strategies developed by the

National Health Service Centre for Reviews and Dissemination (NHS Centre for Reviews and Dissemination, 2001*a*,*b*). In addition, we scrutinised the reference lists of all potentially relevant studies and corresponded with authors of randomised controlled trials for unpublished cost-effectiveness data.

Data extraction and synthesis

The eligibility, design, content, quality and results of all full economic evaluations were judged against standard criteria (Drummond & Jefferson, 1996; NHS Centre for Reviews and Dissemination, 2001*a*). Main between-group comparisons were considered in preference to non-randomised subgroup analyses. All prices were converted to UK pounds and US dollars using a common current exchange rate. A narrative overview of interventions, key design features, results and common methodological strengths and weaknesses was conducted. We paid particular attention to the use of appropriate

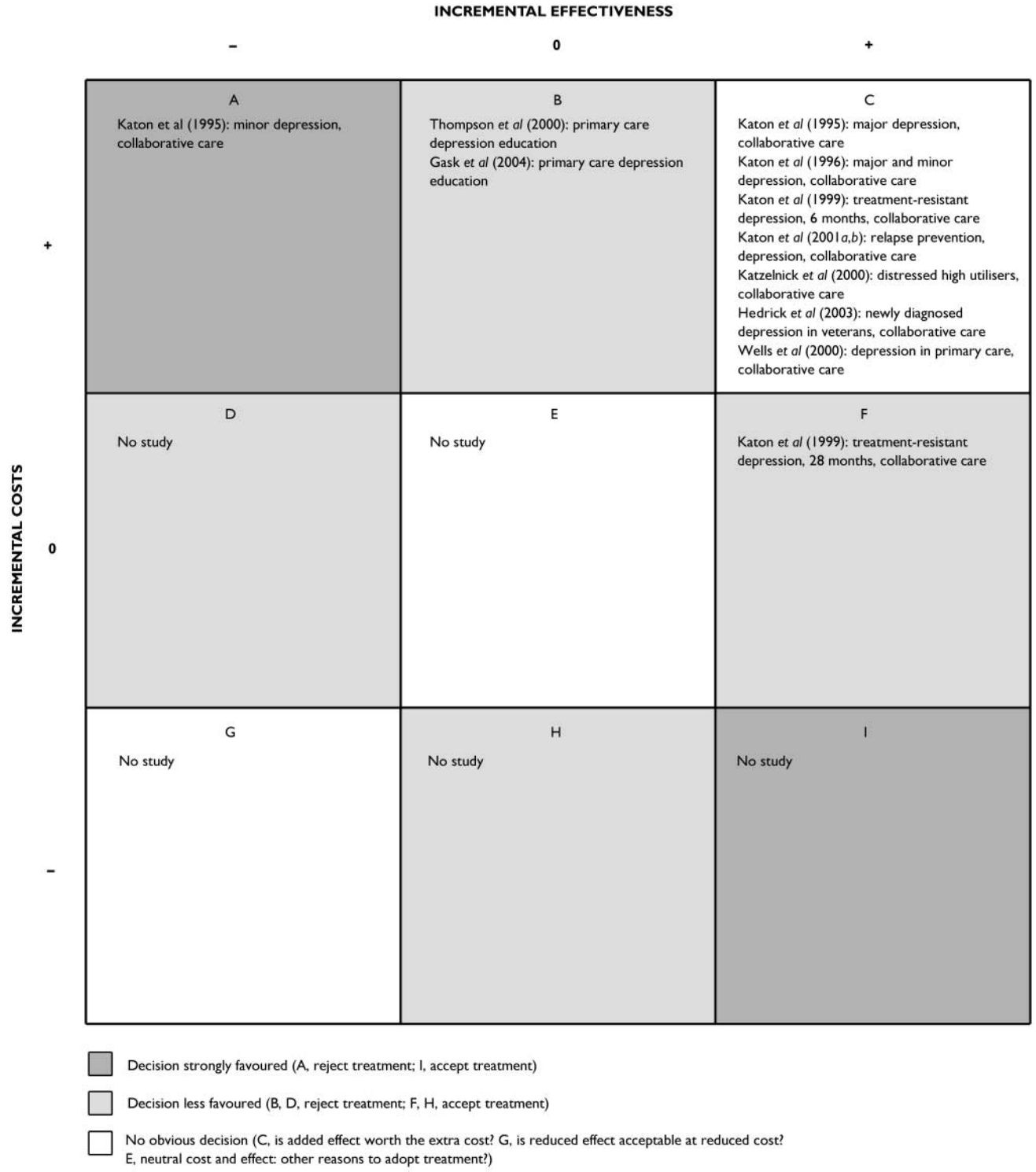

Fig. 1 Permutation matrix for possible outcomes of economic evaluations for study of intervention *v.* comparator following the method proposed by Nixon *et al* (2001). Effectiveness: +, better; 0, same; −, poorer. Cost: +, higher; 0, same; −, lower.

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Table 1 Cost-effectiveness of educational and organisational interventions to improve the management and outcome of depression in primary care settings

Study	Clinical problem, setting and sample size	Intervention and control conditions	Clinical outcomes and follow-up	Cost data	Cost and consequence
Enhanced care for newly diagnosed depression					
Katon *et al* (1995) RCT – individualised Patients randomised CE study (Von Korff *et al*, 1998)	Improved management of depression in newly diagnosed patients willing to take antidepressants US primary care *n*=217 patients	*Intervention*: collaborative management of depression. Multi-faceted intervention: patient education package; physician education about management of depression and monthly case conferences, enhanced consultation and review from specialist psychiatrist. Scheduled follow-up visits with primary care physician and psychiatrist. Review of pharmacy records to check concordance (*n*=108) *Control*: usual care by primary care physician, with usual access to secondary care services (*n*=109)	*Depression*: increased frequency of improvement in I group (50% reduction in SCL score 74.4% I *v.* 43.8% C, $P<0.01$) *Patient satisfaction*: favours I group ($P<0.1$) *Antidepressants*: adequacy of dosage at 90 days better in I (75.5% *v.* 50.0%, $P<0.01$) Seven-month follow-up	*Perspective*: healthcare system *Healthcare costs*: antidepressants; intervention costs; mental health specialist; non-depression primary care costs *Patient and family costs*: not considered *Other non-health sector costs*: not considered	*Type of economic evaluation*: cost-effectiveness analysis *Unit of cost-effectiveness*: cost per successfully treated case of depression *Incremental cost-effectiveness*: £851 ($1592) per successfully treated case (major depression) −£4380 (−$8190) per successfully treated case (minor depression) *Note*: analysis split by major and minor depression. Confidence intervals not calculated, and issue of potentially skewed cost data not accounted for in analysis
Katon *et al* (1996) RCT – individualised Patients randomised CE study (Von Korff *et al*, 1998)	Improved management of depression in newly diagnosed patients US primary care *n*=153 patients	*Intervention*: collaborative management of depression. As above, but specialist collaborative management provided by graduate psychologist, with overall supervision of a psychiatrist to advise on drug management. Management according to a specifically developed manual: brief psychotherapy, problem-solving and patient education (*n*=77) *Control*: usual care by primary care physician, with usual access to secondary care services (*n*=76)	*Depression*: increased frequency of improvement in I group (50% reduction in SCL score: major depression 70.4% I *v.* 42.3% C, $P=0.04$; minor depression 66.7% I *v.* 52.8% C *Satisfaction*: favours I group ($P<0.009$) *Antidepressants*: more patients with adequate dosage of antidepressant at 90 days (major depression 62.1% I *v.* 54.6% C; minor depression 69.6% *v.* 39.5%, $P=0.08$) Seven-month follow-up	*Perspective*: healthcare system *Healthcare costs*: antidepressants; intervention costs; mental health specialist; non-depression primary care costs *Patient and family costs*: not considered *Other non-health sector costs*: not considered	*Type of economic evaluation*: cost-effectiveness analysis *Unit of cost-effectiveness*: cost per successfully treated case of depression *Incremental cost-effectiveness*: £503 ($940) per successfully treated case (major depression); £2001 ($3741) per successfully treated case (minor depression) *Note*: analysis split by major and minor depression. Confidence intervals not calculated, and issue of potentially skewed cost data not accounted for in analysis

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Table 1 (*Continued*)

Study	Clinical problem, setting and sample size	Intervention and control conditions	Clinical outcomes and follow-up	Cost data	Cost and consequence
Enhanced care for newly diagnosed depression					
Katzelnick *et al* (2000) CE study (Simon *et al*, 2001*b*) RCT – clustered Practices randomised No unit of analysis error	High utilisers of medical care with high probability of undiagnosed depression US primary care *n*=163 practices; 407 patients	*Intervention*: depression management programme. Physician education about management of depression. Patient education (booklet and video). Physician guidelines on pharmacotherapy. Depression management coordinated by primary care mental health worker – meetings and telephone follow-up given. Psychiatrist support for patients not responding to treatment (*n*=218) *Control*: usual care (*n*=189)	*Depression*: HRSD improvement scores better at all follow-up in I group (−9.2 points *v.* −5.6, $P<0.001$). Percentage showing 50% improvement at 12 months (53.2% *v.* 32.8%, $P<0.001$) *HRQoL*: favours I ($P<0.05$ on SF–20) *Antidepressants*: more adequate antidepressant therapy in I (69.3% *v.* 18.5% obtained at least 3 prescriptions, $P<0.001$) 12-month follow-up	*Perspective*: healthcare system *Healthcare costs*: antidepressants; intervention costs; mental health specialist; non-depression primary care costs. Mental health out-patient and in-patient costs. Separate evaluations considering (1) out-patient depression treatment costs alone; (2) plus in-patient health service costs; (3) plus time in treatment costs *Patient and family costs*: time in treatment costs estimated from age/gender predicted wages *Other non-health sector costs*: not considered	*Type of economic evaluation*: cost-effectiveness analysis *Unit of cost-effectiveness*: cost per depression-free day *Incremental cost-effectiveness:* (1) out-patient health services costs £11 ($21, 95% CI 11–38) per depression-free day (2) plus in-patient health services £22 ($41, 95% CI 16–81) per depression-free day (3) plus time in treatment costs £28 ($52, 95% CI 17–108) per depression-free day
Simon *et al* (2000) CE study (Simon *et al*, 2000) RCT – individualised Patients randomised No unit of analysis error	Appropriate management of newly diagnosed depression in primary care US primary care *n*=613 patients with depression	*Intervention*: 1. Feedback. Clinicians received computerised feedback of drug use and a recommendation from management algorithm (e.g. recommendation to increase sub-therapeutic dosage) (*n*=221) 2. Care management. As above plus telephone support and treatment monitoring offered by care manager (*n*=196) *Control*: usual care by primary care physician (*n*=196)	*Depression*: Increased frequency of improvement in care management group *v.* control (50% reduction in SCL score, OR=2.22, 95% CI 1.31–3.75) *Antidepressants*: more frequent adequate antidepressant dose in care management group compared with control (OR=1.99, 95% CI 1.23–3.22). No benefit for feedback *v.* control Six-month follow-up	*Perspective*: healthcare system *Healthcare costs*: antidepressants; intervention costs; mental health specialist; non-depression primary care costs. Separate evaluations considering (1) out-patient depression treatment costs alone; (2) total health service costs; (3) plus time in treatment costs *Patient and family costs*: time in treatment costs estimated from age/gender predicted wages *Other non-health sector costs*: not considered	*Type of economic evaluation*: cost-effectiveness analysis *Unit of cost-effectiveness*: cost per depression-free day *Incremental cost-effectiveness*: £7 ($13) per depression-free day *Note*: based upon unpublished cost-effectiveness estimate from the author – confidence intervals not available

(*Continued*)

Enhanced care for newly diagnosed depression

Rost *et al* (2001) CE study (Pyne *et al*, 2003) RCT – clustered Practices randomised No unit of analysis error	Management of depression in primary care practices without onsite mental health specialists US primary care *n*=12 practices, 479 patients	*Intervention*: QuEST. Clinician education. Practice nurse given brief training in managing depression. Administrative staff trained to screen for depression. Nurse coordinated and monitored care of patients according to protocol (*n*=6) *Control*: recruitment by screening by administrative staff and usual care by primary care physicians (*n*=6)	*Depression*: improved depression scores in 1 (CES–D scale 8.2 points 95% CI 0.2–16.1) *Antidepressants*: more frequent adequate antidepressant dose in QuEST (1 36.1% *v*. C 9.8%, *P*=0.0003) Nine-month follow-up *Note*: only patients with no recent treatment for depression included in economic evaluation (*n*=211)	*Perspective*: societal *Healthcare costs*: primary care visits; depression and non-depression primary care costs; antidepressants; intervention costs – training and implementation; mental health specialist and emergency room costs *Patient and family costs*: time and transportation costs using self-reported wages and minimum wages for unemployed *Other non-health sector costs*: including lost productivity – not considered	*Type of economic evaluation*: cost–utility analysis *Unit of cost-effectiveness*: cost per QALY. QALYs calculated from VAS scales and a transformation of the SF–36 (Brazier *et al*, 1998) *Incremental cost-effectiveness*: £8269 ($15 463) per QALY. Cost-effectiveness acceptability curves – probability <$20 000, *P*=0.65; <$50 000, *P*=0.91
Wells *et al* (2000) CE study (Schoenbaum *et al*, 2001) RCT – clustered Clinical practices randomised No unit of analysis error	Enhanced management of depression in primary care in line with US guidelines US primary care *n*=7 practices, 48 clinics, 181 clinicians, 27 332 people screened, 1356 with depression enrolled	*Interventions*: 1. Quality improvement – medications. Patients screened for depression. Nurse specialists diagnose and follow-up patients in conjunction with primary care physician and with specialist support. Nurses supervise drug treatment. Educational intervention to clinicians on guidelines and management (*n*=424) 2. Quality improvement – therapy As above, but nurse encourages patients to receive cognitive–behavioural therapy. No monitoring of medication by nurses (*n*=489) *Control*: Guidelines (Agency for Health Care Policy Research, 1993) disseminated to clinicians by post (*n*=443)	*Depression*: fewer patients with confirmed depression at 6 months (1 1 and 2 combined *v*. C 39.9% *v* 49.9%, *P*=0.00 1; CES-D 50% reduction) and at 12 months (*P*=0.03). No difference in incidence of depression at 24 months *HRQoL*: Small benefit for 1 2 compared with C in SF–12 HRQoL, but not sustained at 24 months *Global outcome*: fewer with global poor outcome in 1 2 at 24 months (1 1 37%; 1 2 27%; C 35%, *P*=0.02) *Antidepressants*: more frequent adequate dose of antidepressants in both groups at 6 months (*P* < 0.00 1) and at 12 and 24 months (1 1 44.5% *v* 1 2 33.5% *v* C 29.2%, *P*=0.04). Less frequent use of minor tranquillisers Follow-up to 5 years. Economic evaluation to 24 months	*Perspective*: societal *Healthcare costs*: primary care visits; depression and non-depression primary care costs; antidepressants; intervention costs – screening; training and implementation; mental health specialist and emergency room costs. In-patient costs excluded *Patient and family costs*: time and transportation costs using self-reported wages and minimum wages for unemployed *Other non-health sector costs*: including lost productivity – not considered	*Type of economic evaluation*: cost–utility analysis *Unit of cost-effectiveness*: cost per QALY. QALYs calculated from the SF–12 (Lenert *et al*, 2000) and number of depression-free days (Lave *et al*, 1998) *Incremental cost-effectiveness*: quality improvement medications by SF–12 method £19 483 ($36 434) per QALY (confidence interval not given). By depression- free days method, 95% CI $15 331 to $30 663 QI therapy by SF–12 method £11 486 ($21 478) per QALY (confidence interval not given). By depression-free days method, 95% CI $9478 to $18 953

(*Continued*)

Table 1 (*Continued*)

Study	Clinical problem, setting and sample size	Intervention and control conditions	Clinical outcomes and follow-up	Cost data	Cost and consequence
Enhanced care for newly diagnosed depression					
Hedrick *et al* (2003) CE study (Liu *et al*, 2003) RCT – individualised	Improved management of depression in newly diagnosed patients US primary care – Veterans Affairs, older and male patient predominance *n*=354 patients	*Intervention*: stepped collaborative care. Clinician education; patient education (video and workbook); weekly treatment plan and specialist review at 6 and 12 weeks; care coordination by social worker. Computerised pharmacy data. Stepped up to more care as necessary (*n*=168) *Control*: usual primary care with access to consultation/liaison psychiatric care (*n*=186)	*Depression*: SCL significantly better in I at 3 months ($P<0.25$); better but borderline significance at 9 months *Antidepressants*: improved concordance with antidepressants in I group at 3 months and 9 months (80% *v.* 62%, $P<0.0001$) *HRQoL*: significant improvements in mental component summary of SF–36 at 3 months and 9 months ($P<0.05$) Nine-month follow-up	*Perspective*: healthcare system *Healthcare costs*: antidepressants; intervention costs; mental health specialist; non-depression primary care costs. Separate evaluations considering (1) out-patient depression treatment costs alone; (2) total out-patient costs; (3) total health service costs *Patient and family costs*: not considered *Other non-health sector costs*: not considered	*Type of economic evaluation*: cost-effectiveness analysis *Unit of cost-effectiveness*: cost per depression-free day *Incremental cost-effectiveness*: (1) out-patient depression treatment costs £13 ($24) per depression-free day (95% CI −$105 to $148) (2) total out-patient costs £18 ($33) per depression-free day (95% −$106 to $232) (3) total healthcare costs £1 ($2) per depression free day (95%CI −$254 to $398)
Enhanced care for treatment-resistant depression					
Katon *et al* (1999) CE study (Katon *et al*, 2002; Simon *et al*, 2001*a*) RCT – individualised Patients randomised	Management of patients with depression (anti-depressant already initiated) not responding to 8 weeks usual care by primary care physician US primary care n=228 patients	*Intervention*: stepped collaborative care. Patient education (book and video). Scheduled visits (×2) with psychiatrist within a primary care setting. Ongoing advice to patient and primary care physician about ongoing progress and management. Psychiatric review of automated pharmacy data (*n*=114) *Control*: usual care by primary care physician (*n*=114)	*Depression*: increased frequency of recovery in I group (50% reduction in SCL score RR=1.42 95% CI 1.02–2.03, NNT=8) over 6 months *Antidepressants*: more frequent adequate antidepressant dose in I compared with C (RR=1.43 95% CI 1.16–1.78 NNT=5) over 6 months *Satisfaction*: favours I group ($P=0.4$) *HRQoL*: no significant improvement of social function ($P=0.10$) and role limitation ($P=0.94$) of SF–36 sub-scales and SDS scores ($P=0.10$) Six-month and 28-month follow-up	*Perspective*: healthcare system *Healthcare costs*: antidepressants; intervention costs; mental health specialist; non-depression primary care costs. Separate evaluations considering (1) out-patient depression treatment costs alone; (2) total out-patient costs; (3) total health service costs *Patient and family costs*: not considered *Other non-health sector costs*: not considered	*Type of economic evaluation*: cost-effectiveness analysis *Unit of cost-effectiveness*: cost per depression-free day *Incremental cost-effectiveness*: out-patient depression treatment costs £11 ($21) per depression-free day (95% CI $8 to $126) over 6 months Total out-patient costs £14 ($26) per depression-free day (95% CI −$10 to $213) over 6 months Total healthcare costs £19 ($35) per depression-free day (95% CI −$52 to $388) over 6 months Longer-term (28-month) follow-up showed continued benefit for collaborative care, and no significant difference in costs for any of the above cost perspectives

(*Continued*)

Enhanced care for depression in remission (relapse prevention)					
Katon *et al* (2001*a*) CE study (Simon *et al*, 2002) RCT – individualised Patients randomised	Prevention of relapse in patients with recurrent depression, currently in remission US primary care *n*=386 patients	*Intervention*: patient education (video and leaflet); 2 visits from a depression specialist (nurse practioners, social worker or psychologist); personalised relapse prevention plan; telephone follow-up (symptom monitoring and medication adherence); monitoring of pharmacy records (*n*=194) *Control*: usual care (*n*=192)	*Depression*: improved and sustained SCL score improvement over 12 months (*P*=0.02), but no difference in relapse rates (I 35% *v.* C 34.6%) *Antidepressants*: increased concordance with medications (OR=1.91, 95% CI 1.37–2.65). Increased proportion with adequate dosage (OR=2.08 95% CI 1.41–3.06) Twelve-month follow-up	*Perspective*: healthcare system *Healthcare costs*: antidepressants; intervention costs; mental health specialist; non-depression primary care costs. Separate evaluations considering (1) out-patient depression treatment costs alone; (2) total out-patient costs; (3) total health service costs *Patient and family costs*: not considered *Other non-health sector costs*: not considered	*Type of economic evaluation*: cost-effectiveness analysis *Unit of cost-effectiveness*: cost per depression-free day *Incremental cost-effectiveness*: (1) out-patient depression treatment costs £13 ($24) per depression-free day (95% CI −$59 to $496) (2) total out-patient costs £8 ($15) per depression-free day (95% CI −$35 to $248) (3) total healthcare costs £0.5 ($1) per depression-free day (95% CI −$134 to $344)
Educational strategies targeted at healthcare professionals					
Thompson *et al* (2000) CE study (Thompson *et al*, 2000) RCT – clustered Practices randomised No unit of analysis error	Recognition and management of depression in line with clinical guidelines UK primary care *n*=59 practices; 169 physicians	*Intervention*: educational materials; educational meetings; educational outreach (*n*=29) *Control*: usual care (educational meetings delayed until after intervention period) (*n*=30)	*Depression*: no improvement in the recognition of depression (sensitivity OR=1.00, 95% CI 0.73–1.37); specificity OR=0.97, 95% CI 0.70–1.34) No increase in proportion improving (OR=1.23, 95% CI 0.84–1.79) or remaining 'cases' (OR=0.82, 95% CI 0.55–1.21) Six-month follow-up	*Perspective*: healthcare system *Healthcare costs*: drug costs; costs of delivering educational intervention *Patient and family costs*: not considered *Other non-health sector costs*: not considered	*Type of economic evaluation*:cost-effectiveness analysis with equal outcome (=cost-minimisation analysis) *Unit of cost*: non-significant change in mean drug costs − £3 ($6) per patient (*P*=0.66). Costs of intervention $313 per practice *Incremental cost-effectiveness*: NA – cost-minimisation study and assume equal outcome
Gask *et al* (2004) RCT clustered PCPs randomised No unit of analysis error	Management of patients with already recognised depression UK primary care *n*=38 clinicians; 395 patients	*Intervention*: 10 h educational intervention (skills-based) on the management of depression using role-play, written materials, video skills assessment (*n*=19 PCPs, 216 patients) *Control*: no training offered until after the trial (*n*=19 PCPs, 179 patients)	*Depression*: no significant difference on either HRSD or GHQ at 2, 6 or 12 months *HRQoL*: SF–36 – no significant difference on most sub-scales, except health perception and role limitation at 12 months ($P < 0.05$) *Patient satisfaction*: improved listening skills from PCPs reported Twelve-month follow-up	*Perspective*: healthcare system *Healthcare costs*: drug costs; health service use (primary and secondary care; specialist and non-specialist) *Patient and family costs*: not considered *Other non-health sector costs*: not considered	*Type of economic evaluation*: cost-effectiveness analysis with equal outcome (=cost-minimisation analysis) *Incremental cost-effectiveness*: NA – cost-minimisation study and assume equal outcome

C, control: CE, cost-effectiveness; CES–D, Center for Epidemiologic Studies – Depression: GHQ, General Health Questionnaire; HRQoL, Health-Related Quality of Life; HRSD, Hamilton Rating Scale for Depression; I, intervention; NA, not applicable; NNT, number needed to treat; PCP, primary care physician; QALY, quality-adjusted life-year; QI, quality improvement; QuEST, Quality of End-of-life Care and Satisfaction with Treatment; RCT, randomised controlled trial; RR, relative risk; SCL, Symptom Check List; SDS, Self-rating Depression Scale; SF–12 (20, 36) 12-item (20, 36) Short Form; VAS, visual analogue scale; US, United States.

methods to generate confidence intervals around cost-effectiveness ratios (Efron & Tibshirani, 1993) and to calculate probabilistic interpretations using cost-effectiveness thresholds and acceptability curves (Fenwick *et al*, 2002). Only confidence intervals and cost-effectiveness acceptability curves based upon an appropriate method were reported. We also examined whether studies had accounted for clustering when clinics and primary care physicians were the unit of randomisation (Ukoumunne *et al*, 1999). Failure to account for clustering within practices ('unit of analysis error') can produce spuriously tight confidence intervals and potentially misleading results (Thomas *et al*, 2003).

Traditional quantitative methods of synthesising clinical data such as meta-analysis are difficult to apply to economic evaluations, and ideally require individual patient-level data which are rarely available to researchers (Petitti, 2000; Bower *et al*, 2003). Instead, we used the schematic method of data synthesis proposed by Nixon *et al* (2001) and recommended in the guidelines issued by the NHS Centre for Reviews and Dissemination (2001*b*). This method of analysis represents incremental cost and incremental effectiveness as a tabular refinement of the cost-effectiveness plane (Black, 1990), known as a 'permutation plot' (Birch & Gaffni, 1996).

Briefly, the permutation plot visually presents nine possible outcomes (see Fig. 1), and links to the issues of technical and allocative efficiency (Donaldson *et al*, 2002). Interventions that are technically efficient (e.g. increased effectiveness at reduced cost) or inefficient (e.g. increased cost with reduced clinical effectiveness) can be quickly identified. Studies that raise questions of allocative efficiency and require decisions about opportunity costs and resource allocation (e.g. increased effectiveness obtained at increased cost, or reduced effectiveness obtained at reduced cost) are also identified. In constructing the permutation plot we used reported point estimates of the incremental cost-effectiveness ratio (ICER) in the first instance. Where ICERs were not available, and incremental cost and incremental effect were presented separately, we used these data to position studies within a specific permutation matrix sector. Where incremental cost data, incremental effectiveness data or incremental cost-effectiveness ratios were given with confidence intervals, we plotted only point estimates in the permutation matrix, and highlighted confidence intervals in the data tables and in the text of our review. Since cost data are often skewed (Briggs & Gray, 1998), we report only differences and confidence intervals where an appropriate method of analysis (such as bootstrapping) was used to account for skewness, and highlight where the issue of potentially skewed cost data might have been ignored in the tables.

RESULTS

From 5873 references, our searches identified 11 full economic evaluations based upon randomised designs, providing clinical and cost-effectiveness estimates for 4757 patients with depression (Von Korff *et al*, 1998; Simon *et al*, 2000, 2001*a*,*b*, 2002; Thompson *et al*, 2000; Schoenbaum *et al*, 2001; Liu *et al*, 2003; Pyne *et al*, 2003; Gask *et al*, 2004). The details and results of each of these studies are presented in Table 1 and summary cost-effectiveness data are shown in the permutation plot (Fig. 1).

Models of care

The majority of studies were economic evaluations of models of enhanced care for depression, based upon collaborative care models, and were conducted within the US healthcare system (Von Korff *et al*, 1998; Simon *et al* 2000, 2001*a*,*b*, 2002; Schoenbaum *et al*, 2001; Liu *et al*, 2003; Pyne *et al*, 2003). Two studies, conducted in the UK, evaluated the clinical and cost-effectiveness of a multidisciplinary primary care educational package designed to improve the quality of care or to implement depression management guidelines (Thompson *et al*, 2000; Gask *et al*, 2004). The majority of economic evaluations were cost-effectiveness analyses, with two cost–utility analyses (Schoenbaum *et al*, 2001; Pyne *et al*, 2003).

Enhanced care was offered for the management of a newly diagnosed episode of depression in 9 of the 11 studies (Von Korff *et al*, 1998; Simon *et al*, 2000, 2001*a*,*b*, 2002; Thompson *et al*, 2000; Schoenbaum *et al*, 2001; Liu *et al*, 2003; Pyne *et al*, 2003; Gask *et al*, 2004), with additional studies for treatment-resistant depression (Simon *et al*, 2001*a*) and relapse prevention (Simon *et al*, 2002). Interventions generally involved some form of clinical practice guideline, with a range of implementation strategies of varying intensity. For example, one study involved the use of brief telephone contact by non-specialist nurses to facilitate concordance with medication, to monitor progress and to coordinate follow-up (Simon *et al*, 2000). In other strategies, such as collaborative and stepped care programmes, a case manager coordinated care between primary care physicians and specialists, while offering brief problem-focused psychosocial interventions (Von Korff *et al*, 1998). The most comprehensive intervention was the Partners in Care study, which included screening, clinician and patient education, guideline dissemination, case management and enhanced access to specialist care, including cognitive–behavioural therapy (Schoenbaum *et al*, 2001).

Details of economic evaluations

The majority of studies examined cost and consequence from the perspective of the healthcare system or third-party payer. Costs generally included all drug, depression and non-depression-related primary care costs, together with the costs of specialist referral. Several studies considered out-patient depression treatment costs alone, before broadening the perspective of the evaluation to include first all out-patient treatment costs and then all health service costs (e.g. Simon *et al*, 2001*a*). Some studies broadened the perspective of the economic evaluation by studying patient and carer expenses and lost earnings through time in treatment (Schoenbaum *et al*, 2001; Pyne *et al*, 2003). No study considered unemployment benefits or lost earnings of patients as a consequence of illness, or wider non-healthcare costs such as social security benefits and lost earnings of carers. The period of follow-up and time horizon of the economic evaluations was generally 6–12 months, although two studies did report cost and effectiveness data at 24 months (Schoenbaum *et al*, 2001) and 28 months (Katon *et al*, 2002).

There was some degree of consistency between studies in terms of the unit of cost-effectiveness. Several studies (Simon *et al*, 2000, 2001*a*,*b*, 2002) reported incremental cost per depression-free day. Two cost–utility studies (Schoenbaum *et al*, 2001; Pyne *et al*, 2003) presented cost per quality-adjusted life-year (QALY) estimates by combining population utility estimates with patient-level rating scores on the short form instruments (Brazier *et al*, 1998; Sugar *et al*, 1998; Lenert *et al*, 2000). The degree of uncertainty around estimates of

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cost-effectiveness was expressed within confidence limits in several studies, calculated through bootstrap analysis (Efron & Tibshirani, 1993), or expressed through cost-effectiveness acceptability curves (Fenwick *et al*, 2002; see Table 1).

Details of cost-effectiveness estimates

The great majority of studies (9 out of 11) demonstrated improved clinical outcomes for depression management, and all demonstrated increased point estimates of costs associated with caring for depression. These results are summarised in the permutation plot (Fig. 2).

Enhanced care programmes for newly diagnosed depression

We found seven randomised economic evaluations (Von Korff *et al*, 1998; Simon *et al*, 2000, 2001*a*,*b*, 2002; Schoenbaum *et al*, 2001; Liu *et al*, 2003; Pyne *et al*, 2003).

Collaborative care approaches attracted increased treatment costs associated with delivering the intervention and increased treatment costs in terms of increased primary care visits, increased use of antidepressant medication, and access to secondary care. When considering primary care depression treatment costs alone, estimates ranged from £7 ($13, no confidence interval given) per depression-free day (Simon *et al*, 2000) to £13 ($24, 95%CI −105 to 148) per depression-free day (Simon *et al*, 2002). When the perspective of the evaluation was broadened in two studies (Simon *et al*, 2001*b*; Liu *et al*, 2003), there was some suggestion that increased costs associated with the intervention might be partially offset through reduced use of other services, reducing the overall cost per depression-free day. In no study was cost-offset through reduced healthcare utilisation of an extent and magnitude to make the overall programme cost-saving and dominant.

In terms of studies examining cost per QALY using tariffs from the short form instruments (Brazier *et al*, 1998; Lenert *et al*, 2000), estimates ranged from £8269 ($15 463, confidence interval not given) per QALY for a nurse-delivered case management approach (Pyne *et al*, 2003) to £19 483 ($36 467, confidence interval not given) per QALY for a complex intervention to enhance medication management (Schoenbaum *et al*, 2001). Using a different method for calculating QALYs (ascribing quality-adjusted weights to the number of depression-free days; Lave *et al*, 1998) in this study (Schoenbaum *et al*, 2001), 95% confidence intervals for case management based around medication ranged from £8190 to £16 380 ($15 331 to $30 663), and for nurse-delivered therapy and case management from £5063 to £10 124 ($9478 to $18 953).

In a series of cost-effectiveness ratio acceptability estimates (Pyne *et al*, 2003) using cost-effectiveness acceptability thresholds, for a nurse-delivered case management approach there was a 65% probability that the cost-effectiveness of the intervention was less than $20 000 per QALY and a 91% probability that it was less than $50 000 per QALY.

Enhanced care for treatment-resistant depression

We found one randomised economic evaluation (reported in two papers: Simon *et al*, 2001*a*; Katon *et al*, 2002).

This stepped care approach, whereby enhanced care was reserved for those who had not responded to initial management by their general practitioner, attracted increased treatment costs in terms of increased primary care visits, increased use of antidepressant medication, and access to secondary care (Simon *et al*, 2001*a*). When out-patient costs alone were considered, improved outcome was achieved at a cost of £11 ($21, 95% CI 8 to 126) per depression-free day over 6 months. There was no evidence of cost offset when the perspective of the intervention was broadened to include total out-patient costs – £14 ($26, 95% CI −10 to 213) per depression-free day – or total healthcare costs – £19 ($35, 95% CI −52 to 388) per depression-free day. Longer-term follow-up over 28 months from this same trial (Katon *et al*, 2002) demonstrated a persistent clinical effect, and cost differences between groups had become non-significant. However, the follow-up was limited by attrition and the low statistical power of this single study made it difficult to interpret this non-significant difference in costs.

Enhanced care to prevent relapse in recurrent depression

We found one randomised economic evaluation (Simon *et al*, 2002). Case management targeted at those with recurrent but remitted depression produced improved depression outcomes at 12 months. This intervention attracted increased treatment costs in terms of increased primary care visits, increased use of antidepressant medication, and access to secondary care (Simon *et al*, 2002). When out-patient costs alone were considered, improved outcome was achieved at a cost of £13 ($24, 95% CI −35 to 496) per depression-free day over 12 months. There was some suggestion of cost offset when the perspective of the intervention was broadened to include total out-patient costs – £8 ($15, 95% CI −35 to 248) per depression-free day – or total healthcare costs – £0.5 ($1, 95% CI −52 to 388) per depression-free day. However, wide confidence intervals prevented firm conclusions in this respect.

Clinician education strategies

We found two randomised economic evaluations (Thompson *et al*, 2000; Gask *et al*, 2004). These studies used a purely educational approach (Thompson *et al*, 2000; Gask *et al*, 2004) and showed no impact on the improved management or outcome of depression, but attracted increased costs associated with the educational intervention. This is clearly ineffective and technically inefficient.

DISCUSSION

The main finding of this review is that there is a large and rigorous body of clinical and economic research into the enhanced management of depression in primary care. Enhancements of care, such as case management and collaborative care, mostly produce improved outcomes but are associated with increased direct healthcare costs over the short term (Von Korff *et al*, 1998; Simon *et al*, 2000, 2001*a*,*b*, 2002; Schoenbaum *et al*, 2001; Liu *et al*, 2003; Pyne *et al*, 2003). Educational strategies did not lead to improved clinical outcomes and were associated with increased costs (Thompson *et al*, 2000; Gask *et al*, 2004). Several issues deserve further consideration.

First, the perspective of all these evaluations was that of the healthcare provider and healthcare system. Depression has profound economic consequences, in terms of direct and indirect costs both to the individual and to wider society (Greenberg *et al*, 2003; Thomas & Morris, 2003), and a consideration of these perspectives is generally more useful to policy makers (Gold *et al*, 1996). There is a possibility that this broader economic perspective might demonstrate

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a higher degree of cost offset and technical efficiency, and there was some evidence from some evaluations that might indeed be the case (e.g. Simon *et al*, 2002; Liu *et al*, 2003). There is now emerging evidence from randomised controlled trials (e.g. Schoenbaum *et al*, 2001; Rost *et al*, 2004) that unemployment is reduced and economic productivity increased as a consequence of case management approaches. These effects deserve to be incorporated into future randomised economic evaluations. Similarly, most of the studies examined cost-effectiveness over a 6- to 12-month perspective. One study that examined costs and consequence over a 28-month period did suggest that excess costs associated with enhanced care in the short term had disappeared over time (Katon *et al*, 2002). This raises the possibility that the benefits of front-loaded intervention costs might be realised over a longer period of follow-up. It should be noted that longer-term clinical benefits of enhanced care for depression have begun to emerge (up to 5 years; Wells *et al*, 2004), although longer-term cost-effectiveness has not been reported at the time of writing. Further research into the longer-term cost and consequences is justified.

A second limitation of this research evidence is the failure to produce a common metric in terms of unit of cost-effectiveness to allow comparisons between competing programmes (Torgerson & Rafferty, 1999). A substantial proportion of evaluations used cost per depression-free day as the unit of cost-effectiveness. This measure has intuitive clinical and economic meaning, and might be adopted across interventions. It is also commendable that attempts have been made to incorporate preference-based measures and to establish cost per QALY for certain interventions. The inherent appeal of this measure is the possibility of comparing net benefit across disease categories and interventions, in order to make more rational decisions about resource allocation and prioritisation (Torgerson & Rafferty, 1999). The notion of how best to measure QALYs in the case of depression is far from clear (Sherbourne *et al*, 2001) and some of the findings in this review demonstrate the inconsistency of findings according to the method used. This is an area that deserves further research.

The third and main issue is about deciding whether enhanced care should be funded, based on these cost-effectiveness data. Decision-makers in this case are fortunate in having recourse to a strong body of research literature on cost-effectiveness to use within their decision-making process – in deciding priorities within healthcare systems and within mental health services. The overriding message of this systematic review is that there is a substantial opportunity to improve the outcomes of depression, and that primary care quality improvement strategies involving collaborative care and case management are a strong candidate approach. However, improving depression outcomes will require a substantial investment of funds. When considering cost per QALY estimates, we note that the health benefit that might be expected within a certain cost threshold is comparable with other interventions that are funded from within healthcare systems. In a review of the population-level impact of mental health interventions, Andrews and colleagues (2000, 2004) demonstrated that interventions with similar levels of expected health gain to those presented in this review can substantially reduce the population burden of illness and disability within existing healthcare budgets.

It has now been comprehensively demonstrated that educational interventions have minimal impact on clinical outcomes, unless they are supported by enhancements of care (Gilbody *et al*, 2003). In addition, we have clearly demonstrated that clinician education packages, when delivered alone, are a cost-ineffective strategy – bestowing no improved outcome at an increased cost. Educational strategies only become effective when they are combined with an enhancement of care such as case management. There is no case for further investment in packages based solely upon an educational design. Our review summarises cost-effectiveness data from two randomised studies of educational interventions (Thompson *et al*, 2000; Gask *et al*, 2004), but should also be considered in the context of a much larger body of evidence from randomised trials (Gilbody *et al*, 2003).

Fourth, the vast majority of economic data relating to collaborative care presented within this review are derived from the USA. This raises questions about the degree to which cost-effectiveness estimates of collaborative care and case management can be translated to other healthcare systems and settings. One reason to be cautious about this aspect is the fact that many depression management programmes evaluated within this review have been designed within a US managed-care system. However, evidence is beginning to emerge of the clinical benefits of this method of organising care in European socialised healthcare systems (Vergouwen *et al*, 2005) and in less affluent countries and less well-financed systems (Araya *et al*, 2003). At the time of writing the cost-effectiveness of these clinically effective non-US studies had not been reported. In the interim, technologies are available to examine cost-effectiveness between different healthcare systems, for example by combining clinical effectiveness estimates from these trials with routine service use and cost data from another healthcare setting, using decision modelling (Petitti, 2000). Our review identifies candidate interventions that can be further evaluated from the perspective of other systems and settings.

The final issue relates to the methods that have been used to summarise the cost-effectiveness literature in this review. We used a method of literature synthesis that had hitherto not been applied in this or any other area of mental health. Through the use of extensive literature searches and an explicit framework of considering the quality of the economic evidence, we have collated and summarised a large and important body of research evidence, using systematic review methodology (Gilbody & Petticrew, 1999). Further, through the use of innovative methods of presenting economic data such as the permutation plot (Nixon *et al*, 2001), we believe we have simplified a complex and heterogeneous body of research evidence to make it understandable for both experts and non-experts alike. Unfortunately, the permutation plot loses much of the interesting detail of individual economic studies, such as the distribution of costs and effects, when point estimates only are plotted in sectors of the cost-effectiveness plane. The results of the permutation matrix should therefore be considered alongside more detailed results of individual studies, such as those presented in data tables. However, the communication of complex health economic research to non-expert audiences is essential in ensuring that economic evidence is incorporated into rational healthcare decision-making.

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APPENDIX

Types of economic evaluations

Adapted from NHS Centre for Reviews and Dissemination (2001*a*).

Full economic evaluations are studies in which a comparison of two or more treatments or care alternatives is undertaken and in which both the costs and outcomes of the alternatives are examined.

Cost–benefit analysis

Cost and outcomes are measured in monetary terms and used to calculate net monetary gains or losses (presented as a cost–benefit ratio). Increasingly used in calculating cost–benefit using the net benefit approach: see McCrone *et al* (2004) for an example.

Cost–utility analysis

Measures the benefits of alternative treatments or types of care by using utility measures such as quality-adjusted life-years (QALYs) and may present relative costs per QALY: see Pyne *et al* (2003) in this review for an example.

Cost-effectiveness analysis

Compares interventions with a common or natural outcome (such as depression severity or depression-free days) to discover which produces the maximum outcome for the same input of resources in a given population: see Simon *et al* (2001*a*) in this review for an example.

Cost-minimisation analysis

Assumes equal outcome for alternative treatments and describes which is associated with the lowest cost. Cost-effectiveness analyses based upon trials which demonstrate equal clinical outcomes are *de facto* cost-minimisation analyses: see Gask *et al* (2004) in this review for an example.

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