

REVIEW ARTICLE

Case management to improve major depression in primary health care: a systematic review

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ABSTRACT

Background. Deficits in the care of depression lead to poor medication adherence, which increases the risk of an unfavourable outcome for this care. This review evaluates effects on symptoms and medication adherence of case management in primary health care.

Method. A systematic literature search was performed. The quality of the studies was rated according to the Cochrane Effective Practice and Organization of Care Group (EPOC) criteria. To conduct a subgroup analysis interventions were classified as either 'standard' or 'complex' case management.

Results. Thirteen studies met the inclusion criteria. In a meta-analysis we calculated a standard mean difference/effect size on symptom severity after 6–12 months of -0.40 (95% CI -0.60 to -0.20). Patients in the intervention groups were more likely to achieve remission after 6–12 months [relative risk (RR) 1.39, 95% CI 1.30–1.48]. The relative risk for clinical response was 1.82 (95% CI 1.68–2.05). Patients in intervention groups had better medication adherence than the control group (RR 1.5, 95% CI 1.28–1.86). We found heterogeneous results when assessing effects of different types of intervention.

Conclusions. We conclude that case management improves management of major depression in primary health-care settings.

INTRODUCTION

Depressed individuals experience a significant burden of illness (Ormel *et al.* 1994, 2004). Patients with depression account for 50% higher health-care costs than otherwise comparable patients who are not depressed (Simon & Ormel, 1995). Most depressed patients are

diagnosed and treated by general practitioners (Kamerow, 1986; Ustun & Sartorius, 1995). Depression is the third most common reason for a primary-care consultation (Shah, 1992). To improve primary health-care for chronic conditions a number of problems have to be resolved: discontinuity and fragmentation of the process of care, lack of coordination between different providers, and 'the tyranny of urgency' (Bodenheimer *et al.* 2002). In the case of depression care these deficits lead to frequent interruption or premature termination of drug therapy, which increases the risk of unfavourable depression outcomes (Ahrens & Linden, 1991; Fritze, 1997). Patient-centred approaches

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with a focus on empowerment and self-management have been recommended (Os *et al.* 1999; Bodenheimer *et al.* 2002; Coulter & Elwyn, 2002).

Case management may be one approach to improve depression care. Case management has been defined as 'taking responsibility for following-up patients; determining whether patients were continuing the prescribed treatment as intended; assessing whether depressive symptoms were improving; and taking action when patients were not adhering to guideline-based treatment or when they were not showing expected improvement' (Von Korff & Goldberg, 2001). Case management consists of five essential components: (1) identification of patients in need of services, (2) assessment of the individual patient's needs, (3) developing a treatment plan, (4) coordination of care, and (5) monitoring outcomes and altering care when favourable outcomes are not achieved (Norris *et al.* 2002).

Prior reviews of case management for mental disorders have two limitations for informing care for depressive illness: (1) They have studied heterogeneous target groups, mainly persons with chronic schizophrenia rather than depression (Holloway *et al.* 1995; McGrew & Bond, 1995; Mueser *et al.* 1998; Ziguras & Stuart, 2000; Marshall *et al.* 2001; Marshall & Lockwood, 2002). (2) The reviews did not stratify for heterogeneity of the interventions – especially in intensity of the intervention (Mueser *et al.* 1998; Marshall *et al.* 2001).

A non-systematic review of controlled trials considered what aspects of depression case management improved patient outcomes for (Von Korff & Goldberg, 2001). This review concluded that active follow-up with monitoring of depression status and psychiatric consultation may be effective elements. A systematic review of depression-care programmes also concluded that they were effective and offered similar conclusions about what elements were effective. But its narrative analysis did not attempt to formally evaluate differences in effects depending on intervention components (Gilbody *et al.* 2003). We now conducted a systematic review and a meta-analysis with a clear focus on case-management intervention for depression care. What is the effectiveness (on symptoms and adherence) of case management

to improve the management of major depression in primary-care settings?

METHOD

Search strategy

A systematic literature search was performed in the following databases: MEDLINE (1966–5.2003), EMBASE (1980–5.2003) and the Cochrane Library (2003, 2nd edition). The search strategy combined the MeSH terms: [(mental disorders) *or* (depression)], *and* [(case management) *or* (disease management)] *and* primary health care. Additionally we conducted hand searches in the reference lists of the retrieved papers and consulted experts in the field to obtain studies which were not included in the electronic databases.

Selection criteria

The criteria for considering which studies to include in this review were: (1) Patients with 'major depression' or 'depressive episode' based on DSM-V or ICD-10 criteria, diagnosed by a validated instrument (Berger & Hecht, 2004). (2) Case management as an intervention for continuity of care including at least the systematic monitoring of symptoms. Further elements were possible as coordination and assessment of treatment and arrangement of referrals (Von Korff & Goldberg, 2001; EPOC, 2002). (3) Follow-up should have been for 6–12 months, because antidepressant therapy should be given for at least 6 months to achieve sustainable effects (NICE, 2004). (4) Interventions had to be located in community-based care (EPOC, 2002). (5) Principal outcomes were severity of depression symptoms measured by validated instruments and a change of the patient's adherence to drug treatment (Berger & Hecht, 2004). (6) Study design was the randomized controlled trials design (EPOC, 2002). Studies were excluded when results were available only as abstracts or without a clearly stated method, or if studies were of low methodological quality (see below). We excluded studies with a focus of action on doctors, patients' relatives, in-patients, drug users, homeless people, disabled people; or on depression in special circumstances such as end-of-life or pregnancy. We also excluded studies examining special interventions for primary prevention, screening,

diagnosis, case finding, health education, pharmacotherapy, counselling, psychotherapy, social work and intensive support.

Data extraction

Data were extracted in evidence tables of an adapted standardized EPOC format by one of the authors (J.G.).

Assessment of methodological quality

Methodological quality was independently rated by two authors (J.G. and M.B.) on a 6-point scale: (a) procedure of randomization, (b) randomization unit, (c) homogeneity of study population at baseline, (d) homogeneity of intervention for all participants, (e) quality of outcome assessment, (f) type of analysis. We scored the studies in good (A = 5–6 points), fair (B = 3–4 points), moderate quality (C = 0–2 points) and excluded studies with moderate quality. Principal intervention outcomes assessed were (i) severity of depression symptoms on the symptom scale, (ii) clinical response defined as 50% improvement from baseline on the outcome scale and (iii) remission defined as depression below the symptom threshold on the scale used in the study (e.g. a Hamilton Rating Scale score of <7) (Berger & Hecht, 2004). For medication adherence, we used each studies' definition of 'good adherence' based on data from pharmacy reports, electronic count boxes, or the patients' self-report.

Statistical analysis

We conducted Egger's funnel plot to control for publication bias (Egger *et al.* 1997; Egger & Smith, 1998). We performed meta-analyses because there was no substantial clinical heterogeneity between the included studies in terms of population, underlying conditions, setting, etc. as our selection criteria were narrow. The meta-analyses were based on a 'random effects model', with respect to possible variances between studies (Egger *et al.* 2001). For the statistical calculation we used 'Review Manager 4.1' (Clarke & Oxman, 2003). The overall treatment effect of case management on severity of depression in score symptoms was calculated as the standard mean difference (SMD)/effect size with 95% confidence intervals (CIs) (Glass *et al.*

1981). It is reported in units of standard deviation and is used when all the trials assess the same outcome, but measure it in a variety of scales (Egger *et al.* 2001). Symptom measures are regarded as continuous with a normal distribution. Binary outcomes as remission, response and adherence were calculated as weighted relative risk (RR and 95% CI) (Flechter, 1996). In all meta-analyses we assessed for statistical heterogeneity using the χ^2 test (Egger, 2001).

In total we conducted two subgroup analyses on the effects of age (work in progress and not reported here) and 'intervention complexity' because trends towards a higher effectiveness in more complex interventions are reported by clinical experts and we could not identify a controlled study on direct comparison. The interventions were classified independently as 'complex' and 'standard' case management using the scores shown in Table 1. We used similar statistical instruments as those reported above.

RESULTS

Our electronic search identified 1246 reports. An initial assessment of the titles and abstracts of these papers and our hand searches revealed 234 articles as potentially relevant to the appraisal. After further assessment, 51 studies were obtained in full text. Of these, 13 studies met the final inclusion criteria (Katon *et al.* 1995, 1999; Banerjee *et al.* 1996; Coleman *et al.* 1999; Llewellyn-Jones *et al.* 1999; Peveler *et al.* 1999; Hunkeler *et al.* 2000; Katzelnick *et al.* 2000; Simon *et al.* 2000; Wells *et al.* 2000; Rost *et al.* 2001; Unützer *et al.* 2002; Hedrick *et al.* 2003). The main reasons for exclusion were: not a randomized controlled trial, not conducted in a community-based setting (i.e. primary health-care), less than 50% of the study sample were diagnosed with major depression at baseline. Egger's funnel plot showed a slight asymmetry with a lack of very small studies (Fig. 1).

Methodological quality

Of the 13 included studies, eight were of good (A), and five of fair (B) methodological quality. To measure effects on symptoms, five trials used the Hopkins Symptom Check List SCL-20,

Table 1. Complexity score for case management interventions

Indicators	Criteria	Cut point for complex case management
Number of elements used	Telephone reminder, relatives' support, treatment guidelines, patient pass, outreach visits (1 pt each) Feedback (2 pts)	More than 4 → 1 pt
Integration into health-care delivery system	Focus on process of care Formal (grade 1-4, when 2: → 1 pt) Integration in different health sectors Factual (1-4, when 2: → 1 pt)	When 2 → 1 pt
Case manager's qualifications	Health auxiliary (1 pt) Trained case manager (2 pts) Multi-disciplinary team (3 pts)	When 2 → 1 pt
Patient empowerment	Patient education (1-3, when 3: → 1 pt) Patient self-management (1-3, when 3: → 1 pt)	When 2 → 1 pt
'Complex case management'		When higher than 2 pts

Source: Gensichen et al. (2004).

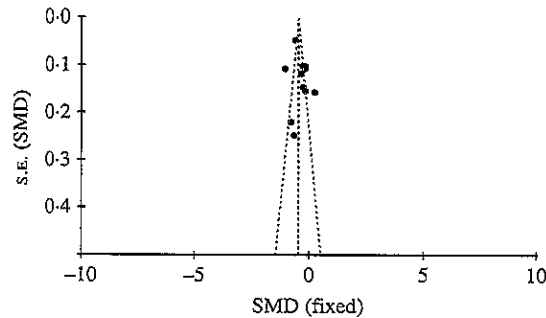


Fig. 1. Funnel plot of included review studies. SMD, Standard mean difference.

three the Center of Epidemiological Studies – Depression Scale, two the Hamilton Depression Rating Scale, and one study each used the following instruments: the Hospital Anxiety and Depression Scale, the Montgomery–Asberg Depression Rating Scale, and the Geriatric Depression Scale. To assess patients' adherence, eight studies employed pharmacy data, three studies used the patients' self-report, and two used an electronic count-box. Most studies were conducted in the US primary health-care system, often in Health Maintenance Organizations (HMOs). All studies offered at least monthly monitoring contact to the intervention patients. In seven trials the case managers were known to the patient. In five studies the case managers were employees of 'call centres'. The case manager typically had a case load of about 20 patients (with the exception of one study with

about 100). Nine studies offered, in addition, three or more elements: e.g. feedback, treatment guidelines or support for the relatives. Seven studies had a follow-up of at least 1 year. Basic pharmacological treatment was given to all patients in all studies, mainly antidepressants, e.g. tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).

Summary results

We pooled the results from 11 studies including data from 4320 patients in a meta-analysis of the severity of depression measured in the symptom scores (Fig. 2) (Katon et al. 1995, 1999; Banerjee et al. 1996; Coleman et al. 1999; Llewellyn-Jones et al. 1999; Hunkeler et al. 2000; Katelnick et al. 2000; Simon et al. 2000; Rost et al. 2001; Unützer et al. 2002; Hedrick et al. 2003). We found no statistical heterogeneity ($\chi^2=85.23$, $df=10$, $p<0.000001$). We calculated a SMD/effect size of -0.40 SMD (95% CI -0.60 to -0.20) after 6–12 months for patients with case management compared to the control group (Table 1). For remission we pooled the data of seven studies including 4584 patients (Banerjee et al. 1996; Katon et al. 1999; Katelnick et al. 2000; Simon et al. 2000; Wells et al. 2000; Rost et al. 2001; Unützer et al. 2002). Patients in the intervention groups had a reduction in their relative risk for lasting depression after 6–12 months of 1.39 (95% CI 1.30–1.48). We found no statistical heterogeneity ($\chi^2=195.34$, $df=6$, $p<0.00001$). For clinical response, we pooled results from five

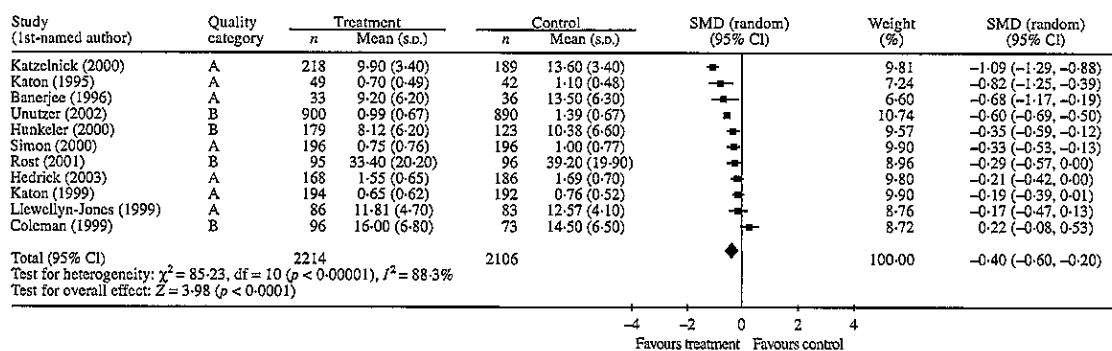


FIG. 2. Effects of case management on symptoms of depression.

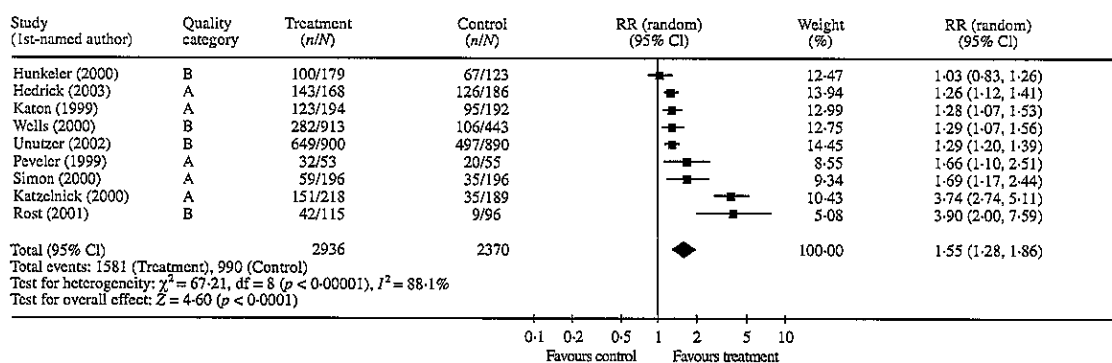


FIG. 3. Effects of case management on adherence.

studies including 3218 patients (Hunkeler *et al.* 2000; Katzelnick *et al.* 2000; Simon *et al.* 2000; Unützer *et al.* 2002; Hedrick *et al.* 2003). In the intervention group, the relative risk for response was 1.82 (95% CI 1.68–2.05). The overall response rate in studies with case management was 45.6% (control group 24.0%). We found no statistical heterogeneity ($\chi^2 = 21.72$, $df = 4$, $p < 0.0002$). For medication adherence, we pooled the data from nine studies ($n = 5306$ patients) (Katon *et al.* 1999; Peveler *et al.* 1999; Hunkeler *et al.* 2000; Katzelnick *et al.* 2000; Wells *et al.* 2000; Simon *et al.* 2000; Rost *et al.* 2001; Unützer *et al.* 2002; Hedrick *et al.* 2003). Patients with case management had improved adherence relative to the control group (RR 1.5, 95% CI 1.28–1.86). In our review we calculated a mean adherence rate of 65.8% in case management and 50.0% in the control group. Again we found no statistical heterogeneity ($\chi^2 = 67.21$) (Fig. 3).

Subgroup analysis

For the subgroup analysis on intervention complexity we classified the study interventions into 'standard' (Katon *et al.* 1995, 1999; Peveler *et al.* 1999; Simon *et al.* 2000; Rost *et al.* 2001) or 'complex' case management (Banerjee *et al.* 1996; Coleman *et al.* 1999; Llewellyn-Jones *et al.* 1999; Hunkeler *et al.* 2000; Katzelnick *et al.* 2000; Wells *et al.* 2000; Unützer *et al.* 2002; Hedrick *et al.* 2003). Both groups were similar in terms of sex, age, severity of depression and in other terms described earlier. The results from three studies with 'standard' case management ($n = 869$ patients) reporting on depression symptoms were pooled (Katon *et al.* 1995, 1999; Simon *et al.* 2000) to a SMD of -0.40 (95% CI -0.64 to -0.17). The results from seven 'complex' interventions ($n = 3093$ patients) were also pooled (Banerjee *et al.* 1996; Coleman *et al.* 1999; Llewellyn-Jones *et al.* 1999; Hunkeler

et al. 2000; Katzelnick *et al.* 2000; Unützer *et al.* 2002; Hedrick *et al.* 2003). Here we calculated a SMD/effect size of -0.38 (95% CI -0.64 to -0.110). We did not find a real difference between 'standard' and 'complex' case management.

DISCUSSION

We identified a number of well-performed randomized controlled trials on case management for patients with major depression. Limitations of our search arose solely from the use of main international databases. MEDLINE captures only 19.5% of the family medicine literature (McDonalds *et al.* 1999; Obst, 2002). It is possible that additional searches in other databases might have retrieved additional studies. However, experts in the field who reviewed the list did not identify missed studies. The first meta-analysis on symptom improvement used data from different depression scales. By using SMD we could summarize and compare effects across studies (Egger, 2001). From these analyses, the most important factor in heterogeneity across studies appeared to be due to the use of different instruments to assess symptom improvement. The second most important factor contributing to between-study heterogeneity was the complexity of the interventions, which was controlled in subgroup analyses discussed below.

Our results suggest the sustainability of therapeutic effects was due to case management as patients in both groups received standard antidepressant pharmacological treatment, with case management introduced in the intervention group only. This positive effect was seen for all outcomes assessed (symptom improvement, remission, response, and adherence). The statistically significant effect of case management reported on symptom improvement in primary health-care with an effect size of 0.40 can be classified as 'small' to 'moderate' (Kazis *et al.* 1989), but assessment of effect size needs to consider that controls were treated. Another primary-care-based non-pharmacotherapeutical intervention: counselling for depressive patients showed a larger short-term effect: weighted mean difference (WMD) = -2.03 , 95% CI $3.82-0.24$, but after 6–12 months the effect was no longer evident (Bower *et al.* 2001). Case

management over the long term (6–12 months) seems to achieve modest sustained effects (WMD = -0.31 , 95% CI -0.36 to -0.26).

The effect on remission of antidepressants *versus* placebo was estimated as absolute risk reduction (ARR) = 0.23 (for TCAs; Wilson *et al.* 2001). Case management *versus* usual treatment (all patients, of course, receive antidepressants) can add an additional risk reduction in the dimension of ARR = 0.13. Comparing relative risk reductions would be misleading in this case because the effect of drug treatment is greater in absolute terms. We conclude that case management provides an additional benefit to the drug therapy. The 'mechanism of action' of case management may be through increased medication adherence. The results of our meta-analysis indicate an effect on improved medication adherence of RR = 1.4. Although adherence assessment is difficult (WHO, 2003), estimated effects of case management are comparable to interventions such as combining educational interventions for patients and clinicians (RR 1.43, 95% CI 1.16–1.78) (Gerrity *et al.* 1999).

A limitation in combining the identified studies is their differing types of randomization (individual and cluster/clinic). Cluster randomization is a commonly used design in primary health-care research to avoid control-group contamination and to permit delivery of case-management services to a defined practice unit (e.g. a clinic). The effects of our review could be overestimated, because in the meta-analysis we could not control for intra-cluster correlation (ICC) (Thomas *et al.* 2003). Data on ICCs were not available for the majority of the included studies. Most of the studies were conducted in US managed care (HMO) settings. Organization and function of primary care in other countries (such as Germany or the UK) probably differ (WHO, 2000), and therefore, the need for continuity and pro-active care served by case management may vary. Nevertheless, in most health-care systems a 'primary source of care' (Starfield, 1998) can be identified, typically the general or family practitioner (Grol *et al.* 2000). When reporting results of subgroup analyses, caution is indicated. Although we did not observe heterogeneity, the statistical power of the χ^2 test of heterogeneity is low (Egger, 2001), therefore, heterogeneity across studies

may be present. Also subgroup analyses are known to produce chance results which need to be confirmed through additional research (Rothwell, 2005). Our results do not provide strong support for the superiority of 'complex' case management over 'standard' case management, but further research on this question is needed. Additional questions for further research include: What qualifications are needed for an effective case manager? Which single elements of case management, such as telephone monitoring, are most effective? In future studies, it would be helpful if case-management interventions were more adequately described. It might also be helpful to use the complexity score presented here or a similar one (e.g. Wagner *et al.* 1996).

CONCLUSION

We conclude case management is an effective intervention to improve the management for patients with major depression in primary health-care. There is a need for further research in different health-care systems. Considering the higher costs of 'complex' case management (Schoenbaum *et al.* 2001) and following the preliminary results of our subgroup analysis, the available evidence is insufficient to recommend 'complex' case management over 'standard' case management. Future studies should focus on requirements of 'complexity' and on 'cost effectiveness' of case management.

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DECLARATION OF INTEREST

None.

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