Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: a preliminary meta-analysis

Guidi J, Fava GA, Fava M, Papakostas GI

CRD summary
The review found that sequential administration of psychotherapy after response to acute-phase pharmacotherapy, either alone or in combination with antidepressant drugs, may prevent relapse or recurrence in major depressive disorder. The authors' cautious conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To assess the efficacy of the sequential integration of psychotherapy and pharmacotherapy in reducing the risk of relapse and recurrence in major depressive disorder.

Searching
MEDLINE, EMBASE, PsycINFO and The Cochrane Library were searched from inception to December 2008; search terms were reported. Reference lists of retrieved studies and reviews were searched. Authors of significant papers and other experts in the field were contacted.

Study selection
Randomised controlled trials (RCTs) that assessed the efficacy of sequential use of psychotherapy after response to acute-phase pharmacotherapy in the treatment of adult patients (>18 years) with major depressive disorder were eligible for inclusion in the review. Primary outcomes were relapse or recurrence rates of depression (as defined in the individual studies) at the longest available follow-up. Studies that did not primarily involve face-to-face delivery of psychotherapy were excluded. Also excluded were studies that included patients with other psychiatric conditions or active medical illness, studies where relapse and recurrence were not identified categorically and studies where continuation and maintenance treatments for major depressive disorder were used (psychotherapy administered during the acute phase).

Participants in the included studies averaged 44.5 years of age and two thirds were female. Participants had a wide range in risk of relapse or recurrence (6% to 90%). Psychotherapy included cognitive-behaviour therapy, cognitive therapy, mindfulness-based cognitive therapy and well being therapy. Sequential psychotherapy was compared with antidepressant medication and clinical management (monitoring medication, reviewing clinical status and providing advice and support if required), clinical management alone or treatment as usual (defined as standard care with no restrictions on the use of pharmacotherapy). In some studies, antidepressant drugs were continued during psychotherapy and in others antidepressant therapy was tapered or discontinued. Treatment duration ranged from eight to 26 weeks. Relapse or recurrence was defined as a major depressive episode by either Diagnostic Symptoms Manual (DSM) IV, DSM-III-R or Spitzer's Research Diagnostic Criteria.

Two reviewers independently selected studies for the review. Disagreements were resolved by consensus.

Assessment of study quality
Three criteria were used to assess studies for quality: random allocation of treatments, blinding of outcome assessment and handling of attrition.

Two reviewers independently assessed studies for quality.

Data extraction
Data were extracted on the risk ratio (RR) of relapse or recurrence and its standard error.

Two reviewers independently extracted data onto a pre-coded form.

Methods of synthesis
Studies were pooled and summary risk ratios and their 95% confidence intervals (CIs) were calculated using a random-effects model. Heterogeneity was assessed with the $X^2$ test. Inconsistency between studies was quantified with the $I^2$ value. Publication bias was assessed by visual inspection of Begg's funnel plot with testing for asymmetry using Egger's test.

Sensitivity analyses tested the robustness of results by excluding each study in turn from the analysis and determining whether treatment effects changed. Meta-regression was used to determine whether certain study characteristics influenced treatment effects. Subgroup analyses were performed to assess effects separately according to whether studies used a continuation of antidepressant drugs during psychotherapy or tapered and discontinued drug therapy.

Results of the review
Eight studies (875 participants) were included in the review. All studies were randomised and assessors were unaware of treatment allocation. Five studies performed intention-to-treat analyses. Two studies retained all their patients. Completers' data were reported in one study. Follow-up ranged from 28 weeks after randomisation to six years after treatment.

Compared to control, sequential use of psychotherapy was associated with a significantly lower risk of relapse or recurrence (RR 0.80, 95% CI 0.66 to 0.96; eight studies with no significant heterogeneity). Sensitivity analyses indicated that one study changed the results to a non-significant trend that favoured sequential psychotherapy. Meta-regression suggested that continuation versus tapering of pharmacotherapy, different types of psychotherapy and different duration of treatment did not markedly influence results.

Subgroup analyses: Compared to continuation of antidepressant medication or treatment as usual, psychotherapy during continuation of antidepressants was associated with a non-significant trend in reducing relapse or recurrence (RR 0.84, 95% CI 0.67 to 1.05; five studies with no significant heterogeneity). Compared to continuation of antidepressants or clinical management, continuation phase psychotherapy while antidepressants were discontinued was associated with significantly lower rates of relapse or recurrence (RR 0.65, 95% CI 0.46 to 0.91, $I^2=52%$; three studies with no significant heterogeneity).

There was no evidence of publication bias in any of the analyses.

Authors' conclusions
The sequential administration of psychotherapy after response to acute-phase pharmacotherapy, either alone or in combination with antidepressant drugs, may prevent relapse or recurrence in major depressive disorder.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared appropriate. Several relevant sources were searched to identify studies. Appropriate methods were used to select studies, extract data and assess studies for quality, which minimised risks of reviewer error and bias. Studies were assessed appropriately for quality and were found to be generally of high quality by the assessed criteria, although allocation concealment was not assessed and sample sizes were small.

Studies were synthesised and heterogeneity was assessed appropriately. Sensitivity analyses, subgroup analyses and meta-regression were used to test the robustness of results to different assumptions and influence of study characteristics. Publication bias was assessed appropriately and no evidence was found.

The authors' cautious conclusions reflect the evidence presented and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that patients with major depressive disorder needed to be motivated to undergo short-term psychotherapeutic treatment while apparently well. This treatment required referral to a specialised psychotherapist.

Research: The authors stated a need for further research to find ways of extending care across multiple phases of major depressive disorder. Research needed to include evaluations of longitudinal efficacy and cost effectiveness of sequenced treatment protocols and include types of psychotherapy other than cognitive-behaviour therapy.
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