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ORIGINAL ARTICLE

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

**J. Guidi[1]*, G. A. Fava[1,2], M. Fava[3,4] and G. I. Papakostas[3,4]**

[1] *Affective Disorders Program, Department of Psychology, University of Bologna, Italy*
[2] *Department of Psychiatry, State University of New York at Buffalo, Buffalo, NY, USA*
[3] *Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA*
[4] *Department of Psychiatry, Harvard Medical School, Boston, MA, USA*

**Background.** Prevention of relapse and recurrence represents an important task in the successful treatment of major depressive disorder (MDD). The aim of this meta-analysis was to examine the efficacy of the sequential integration of psychotherapy and pharmacotherapy in reducing the risk of relapse and recurrence in MDD.

**Method.** Keyword searches were conducted in Medline, EMBASE, PsycINFO and the Cochrane Library from inception of each database to December 2008. Randomized controlled trials examining the efficacy of the administration of psychotherapy after successful response to acute-phase pharmacotherapy in the treatment of adults with MDD were considered for inclusion in the meta-analysis.

**Results.** Eight high-quality studies with 442 patients in a sequential treatment arm and 433 in a control treatment arm were included. The pooled risk ratio (RR) for relapse/recurrence was 0.797 [95% confidence interval (CI) 0.659–0.964] according to the random-effects model, suggesting a relative advantage in preventing relapse/recurrence for the sequential administration of treatments compared with control conditions. Performing subgroup analyses, we found a trend favoring psychotherapy during continuation of antidepressant drugs compared to antidepressants or treatment as usual (RR 0.842, 95% CI 0.674–1.051). Patients randomized to psychotherapy while antidepressants were discontinued were significantly less likely to experience relapse/recurrence compared to controls (RR 0.650, 95% CI 0.463–0.912).

**Conclusions.** We found evidence that the sequential integration of psychotherapy and pharmacotherapy is a viable strategy for preventing relapse and recurrence in MDD. In addition, our findings suggest that discontinuation of antidepressant drugs may be feasible when psychotherapy is provided.

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**Key words**: Major depressive disorder, meta-analysis, psychotherapy, recurrence, sequential treatment.

## Introduction

Major depressive disorder (MDD) is a highly prevalent condition in the general population, and its chronic and recurrent nature is receiving increasing attention. Approximately eight of 10 people with MDD will experience one or more episodes during their lifetime. For some patients, major depressive episodes are separated by many symptom-free years of normal functioning. For others, the episodes become increasingly frequent, accompanied by residual symptoms and functional impairment. This latter course is found to be the more prevalent, in both psychiatric and primary care settings (Depression Guideline Panel, 1993). As a result, prevention of relapse and recurrence represents a crucial task for the successful treatment of depression.

The addition of psychotherapy to pharmacotherapy has been considered to offer a better possibility of improving long-term outcome. The results of an early meta-analysis (Pampallona *et al*. 2004), for example, demonstrated a significant advantage of combined treatment *versus* pharmacotherapy alone in terms of full response [odds ratio (OR) 1.86, 95% confidence interval (CI) 1.38–2.52]. Similarly, in a more recent meta-analytic review (Vittengl *et al*. 2007), patients treated with cognitive therapy plus pharmacotherapy had a 61% chance of better outcome (lack of relapse/recurrence) than those treated with pharmacotherapy

* Address for correspondence: J. Guidi, Psy.D., Department of Psychology, University of Bologna, Viale Berti Pichat, 5, 40127 Bologna, Italy.
(Email: jenny.guidi2@unibo.it)

alone, with the addition of psychotherapy to pharmacotherapy reported to reduce the chance of relapse/recurrence by as much as 23%. Finally, a mega-analysis based on three original randomized clinical trials (de Maat *et al*. 2008) comparing short psychodynamic supportive psychotherapy, antidepressants, and their combination in the treatment of major depression suggested that combined therapy is superior to pharmacotherapy alone, for both symptom reduction and improving quality of life. These analyses, however, did not focus on examining the efficacy of a specific modality of integration of pharmacotherapy and psychotherapy, which is subsumed under the definition of sequential model (Fava *et al*. 2005*a*).

The sequential treatment of mood disorders does not fall within the realm of maintenance strategies, which have the aim of prolonging clinical responses that treatments have obtained (Kupfer, 1992). It is an intensive, two-stage approach that derives from the awareness that one course of treatment with a specific tool (whether pharmacotherapy or psychotherapy) is unlikely to entail solution to the affective disturbances of patients, in both research and clinical practice settings (Fava & Kellner, 1991; Fava, 1999). One type of treatment (e.g. psychotherapy) may thus be used to improve symptoms that the other type of treatment (e.g. pharmacotherapy) was unable to affect. The rationale of this approach is to use psychotherapeutic strategies when they are most likely to make a unique and separate contribution to patient well-being and to achieve a more pervasive recovery. The target of psychotherapeutic work is thus no longer predetermined, but varies according to the nature, characteristics and intensity of residual symptoms.

The presence of residual symptoms despite successful response to therapy seems to be the rule after completion of drug or psychotherapeutic treatment in mood disorders, and has been strongly correlated with poor long-term outcome (Fava, 1999). These findings have led to the hypothesis that residual symptoms upon recovery may progress to become prodromal symptoms of relapse, and that treatment directed toward residual symptoms may yield long-term benefits (Fava & Kellner, 1991).

Another line of evidence potentially supporting the sequential model in mood disorders is the increasing awareness of the role of co-morbidity in treatment outcome and also in functional recovery (Pincus *et al*. 2004; Maj, 2005). In major depression, it has been demonstrated that as many as two-thirds of patients also meet the criteria for another Axis I disorder (particularly anxiety disorders) and one-third have two or more disorders (Zimmerman *et al*. 2002). The presence of anxiety disorders has been shown to predict persistence and recurrence of depressive illness in MDD (Sherbourne & Wells, 1997; Gaynes *et al*. 1999). However, it is unlikely that monotherapy can provide a solution to such complex disturbances, particularly because some forms of co-morbidity may be covered by the acute manifestations of the disorder and become evident only when the most severe symptoms have been abated (Fava, 1999).

The aim of this meta-analysis was to examine the efficacy of the sequential administration of psychotherapy after response to acute-phase pharmacotherapy in reducing the risk of relapse and recurrence in MDD. The relative efficacy of alternative treatment strategies, that is modifications of cognitive behavioral techniques including mindfulness-based cognitive therapy and cognitive behavior treatment of residual symptoms, were also examined, in addition to the advantages of continuing medication during psychotherapy *versus* tapering and discontinuation.

## Method

### *Data sources*

Published reports were identified with the use of electronic database searches. Keyword searches were conducted in Medline, EMBASE, PsycINFO and the Cochrane Library, from inception of each database to December 2008, combining the following terms: 'sequential treatment', 'drugs and psychotherapy', 'combined treatment', 'continuation or maintenance', 'relapse or recurrence and prevention', 'depress* or major depress*', selecting 'adults' and 'randomized controlled trials' as additional limits. Reference lists from relevant studies and reviews were examined for further clinical trials not yet identified. Authors of significant papers and other experts in the field were contacted.

### *Study selection*

Selection of studies was performed independently by two reviewers (J.G. and G.I.P.). Any disagreement was resolved in a meeting between the two reviewers. We selected for (*a*) randomized controlled trials examining (*b*) the efficacy of the sequential use of psychotherapy following response to acute-phase pharmacotherapy in the treatment of (*c*) adult patients (*d*) with MDD. The primary outcome measures were relapse or recurrence rates of depression as defined by study investigators (i.e. reaching a cut-off on any depression symptom rating scale used by authors and/or the occurrence of a defined episode of major depression after remission/recovery in acute-phase treatment) at the longest available follow-up.

We excluded studies if they (*a*) were not randomized controlled trials, (*b*) did not contain original data, or (*c*) did not primarily involve face-to-face delivery of psychotherapy. We also excluded studies in which (*d*) relapse or recurrence rates were not identified categorically. Finally, we excluded clinical trials of (*e*) continuation and maintenance treatments for MDD in which psychotherapy was also administered during the acute phase, so that continuation-phase treatments matched the modality used during the initial phase.

Studies containing (*f*) patients younger than age 18 or that (*g*) focused exclusively on the treatment of patients with bipolar disorder, dysthymic disorder, minor depressive disorder or seasonal affective disorder, and also studies (*h*) including or exclusively focusing on patients with predominant anxiety disorders, schizophrenia or other psychotic disorders, comorbid alcohol or substance use disorders, antisocial personality disorder, borderline personality disorder, or active medical illness were also excluded from this meta-analysis.

### *Data extraction*

Data were extracted independently by both reviewers with the use of a pre-coded form. The following data were extracted from studies meeting criteria for inclusion in the meta-analysis: age, gender distribution, methods used to define and diagnose study participants, and other inclusion criteria (i.e. recovered from a depressive episode or in remission); type of psychological intervention or control condition, number of patients randomized to each treatment arm, treatment duration and assessment times; methods used to define relapse/recurrence and relapse/recurrence rates. The methodological quality of the included trials was assessed independently by both reviewers based on three basic criteria: random allocation of treatments, blinding of outcome assessment and handling of attrition.

### *Data synthesis*

The primary outcome of the meta-analysis was efficacy of the sequential use of psychotherapy after pharmacotherapy, expressed in relapse or recurrence rates. Therefore, the risk ratio (RR) of relapse or recurrence and its standard error (S.E.) were calculated from each study. Examination of the pooled results was performed based on the random-effects model to increase the generalizability of findings because this model is more conservative then the fixed-effects model. An $\alpha$ level of 0.05 was used for hypothesis tests.

In addition to point estimates and CIs, the $Q$ statistic was performed to assess heterogeneity between study results. With this statistic the null hypothesis is tested that effect sizes from each of the studies were similar enough that a common population effect size could be calculated (Cochran, 1954). However, the $Q$ statistic only informs about the presence *versus* the absence of heterogeneity, and it does not report on the extent of such heterogeneity. The $I^2$ statistic, which is an indicator of heterogeneity in percentages, was also calculated. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (Higgins & Thompson, 2002).

The likelihood of significant publication bias was assessed through Begg's funnel plot (Begg, 1994) with testing for asymmetry using Egger's test statistic (Egger *et al*. 1997). Sensitivity analyses were implemented to estimate the influence of each study by deleting each in turn from the analysis and noting the degree to which the size and significance of the treatment effect changed. Meta-regression was performed to investigate how certain characteristics (i.e. drug continuation during psychotherapy, use of alternative psychotherapeutic strategies, treatment duration and time-points to data collection) acted to influence treatment effects. Finally, clinical heterogeneity between studies was explored by performing subgroup analyses. All analyses were conducted using the user-written packages for meta-analysis available in Stata 10.1 (Stata Corporation, USA).

## Results

### *Characteristics of included studies*

The initial search strategies identified 39 articles for potential inclusion in the meta-analysis. Of these, we excluded 11 studies that were duplicate publications or represented reanalyses of data published elsewhere (Fava *et al*. 1994, 1996, 1998*c*; Paykel *et al*. 1999; Scott *et al*. 2000, 2003; Williams *et al*. 2000; Teasdale *et al*. 2002; Petersen *et al*. 2004; Bockting *et al*. 2005, 2008). We excluded seven other studies because they either did not report relapse rates (Barhofer *et al*. 2007; Kingston *et al*. 2007), were not randomized controlled trials (Klerman *et al*. 1974; Kühner *et al*. 1996; Blackburn & Moore, 1997; Kühner, 2005) or focused on telephone-based psychotherapy as opposed to face-to-face sessions (Miller & Weissman, 2002). We also excluded three studies of the sequential use of psychotherapy either because they involved patients who had successfully responded to antidepressant drugs, and then relapsed (Fava *et al*. 2002; Fabbri *et al*. 2007), or because they involved patients who had not

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remitted with acute-phase psychotherapy (Frank *et al*. 2000). Finally, 10 studies were not included because continuation or maintenance-phase treatments matched the modality used during the initial phase, that is they used the traditional, non-sequential design without a sequential comparator arm (Blackburn *et al*. 1981, 1986; Frank *et al*. 1990; Jarrett *et al*. 1998, 2000, 2001; Reynolds *et al*. 1999, 2006; Keller *et al*. 2000; Klein *et al*. 2004).

Therefore, a total of eight studies (Fava *et al*. 1998*b*, 2004; Teasdale *et al*. 2000; Perlis *et al*. 2002; Ma & Teasdale, 2004; Paykel *et al*. 2005; Bockting *et al*. 2006; Kuyken *et al*. 2008) met criteria for inclusion in the meta-analysis. These studies reported relapse and/or recurrence rates for a total of 875 participants (442 patients in a sequential treatment arm, and 433 in a control arm). Participants averaged 44.5 (S.D. = 9.23) years of age, and 66.6% (range 49.5–76%) were female. Selected characteristics of these included studies are presented in Table 1. Three studies compared a sequential treatment arm with antidepressant medication and clinical management (CM) (Perlis *et al*. 2002; Paykel *et al*. 2005; Kuyken *et al*. 2008), three with treatment as usual (TAU) (Teasdale *et al*. 2000; Ma & Teasdale, 2004; Bockting *et al*. 2006), and two with CM alone (Fava *et al*. 1998*b*, 2004). TAU involved standard care as typically provided by the referring agencies (e.g. family doctors or other sources), with no restriction on the use of pharmacotherapy. CM consisted of monitoring medication administration (including tapering antidepressant drugs), reviewing the patient's clinical status, and providing the patient with limited support and advice if necessary, whereas specific interventions (e.g. exposure strategies, diary work, cognitive restructuring) were proscribed.

The methodological quality of these clinical trials was high. In all studies, participants were assigned at random to the conditions, and it was reported that assessors were not aware which treatment patients were assigned to. Intention-to-treat (ITT) analyses were performed in five studies (Teasdale *et al*. 2000; Perlis *et al*. 2002; Ma & Teasdale, 2004; Paykel *et al*. 2005; Kuyken *et al*. 2008), whereas all patients were retained in two studies (Fava *et al*. 1998*b*, 2004), and in one study completers' data only were reported (Bockting *et al*. 2006).

### *The sequential integration of psychotherapy and pharmacotherapy*

We compared the effects of the sequential use of psychotherapy (either alone or in combination with antidepressant medication) with control conditions (Fig. 1). The pooled RR for relapse/recurrence was 0.797 (95% CI 0.659–0.964) in the random-effects model, suggesting a relative advantage in preventing relapse/recurrence (i.e. lower risk of relapse/recurrence) for the sequential administration of treatments compared with both active and non-active controls. Heterogeneity across trials was not statistically significant ($Q = 3.673$, df = 7, $p = 0.817$). The $I^2$ statistic also indicated no significant heterogeneity ($I^2 = 0\%$) among the pooled studies. Both visual inspection of Begg's funnel plot and Egger's test ($p = 0.053$) were not suggestive for the presence of publication bias. A sensitivity analysis was performed to determine the contribution of each study to the overall effect size, and one study (Fava *et al*. 1998*b*) seemed to markedly influence the observed RR for relapse or recurrence. Removing this study from the analysis, we found a non-significant trend in the rates of relapse/recurrence favoring the sequential integration of psychotherapy compared to control conditions (RR 0.823, 95% CI 0.677–1.001), with no significant heterogeneity across trials ($Q = 1.682$, df = 6, $p = 0.947$, $I^2 = 0$).

Performing meta-regression analyses, we did not find any advantage of continuing medication during psychotherapy *versus* tapering and discontinuation (coefficient 0.10, 95% CI −0.111 to 0.321). Modifications of cognitive behavior therapy (CBT), such as mindfulness-based cognitive therapy (MBCT) and CBT of residual symptoms [either alone or supplemented by well-being therapy (WBT)], administered in sequential order, were found to be as effective in reducing relapse/recurrence as standard CBT (coefficient −0.137, 95% CI −0.327 to 0.053). We also tested for the duration of treatment as well as for the length of follow-up, and we did not find significant effects on relapse/recurrence rates among the included studies (coefficient −0.027, 95% CI −0.423 to 0.369; coefficient −0.002, 95% CI −0.666 to 0.662 respectively).

Analyses were also performed in subsamples to examine separately studies involving continuation of antidepressant drugs during psychotherapy and those with tapering and discontinuation.

### *Sequential use of psychotherapy during continuation of antidepressant medication*

Five clinical trials contributed data for this subgroup analysis (Teasdale *et al*. 2000; Perlis *et al*. 2002; Ma & Teasdale, 2004; Paykel *et al*. 2005; Bockting *et al*. 2006). Data showed a non-significant trend favoring the use of psychotherapy during continuation of antidepressant medication in reducing rates of relapse/recurrence compared to active control conditions (i.e. continuation of antidepressant medication or TAU). The pooled RR for relapse was 0.842

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**Table 1.** *Studies included in the meta-analysis*

| Study | Mean age (years) (% female) | Relevant treatment conditions | Treatment duration (weeks) | Relapse or recurrence definition | Length of follow-up | No. of subjects per cell | RR for relapse or recurrence |
|---|---|---|---|---|---|---|---|
| Bockting *et al*. (2006) | 44.7 ± 9.5 (73) | CT + TAU<br>TAU | 8 | MDE (DSM-IV) | 2 years post-randomization | 88<br>84 | 56.8<br>61.9 |
| Fava *et al*. (1998*b*) | 43.7 ± 2.3 (67.5) | CBT of residual symptoms<br>CM | 20 | MDE (RDC) | 6 years after treatment | 20<br>20 | 50<br>75 |
| Fava *et al*. (2004) | 46.9 ± 11.2 (60) | CBT of residual symptoms + WBT<br>CM | 20 | MDE (RDC) | 6 years after treatment | 20<br>20 | 40<br>90 |
| Kuyken *et al*. (2008) | 49.2 ± 11.2 (76.4) | MBCT<br>ADM | 8 | MDE (DSM-IV) | 15 months post-randomization | 61<br>62 | 47.5<br>59.7 |
| Ma & Teasdale (2004) | 44.5 ± 8.9 (76) | MBCT + TAU<br>TAU | 8 | MDE (DSM-IV) | 1 year after treatment | 36<br>37 | 38.9<br>62.2 |
| Paykel *et al*. (2005) | 43.4 ± 10.5 (49.5) | CBT + ADM + CM<br>ADM + CM | 20 | MDE (DSM-III-R) | 6 years post-randomization | 80<br>78 | 60<br>65 |
| Perlis *et al*. (2002) | 39.9 ± 10.3 (54.5) | CT + ADMI<br>ADMI + MM | 26 | MDE (DSM-IV) | 28 weeks post-randomization | 66<br>66 | 6.1<br>7.6 |
| Teasdale *et al*. (2000) | 43.5 ± 9.9 (76) | MBCT + TAU<br>TAU | 8 | MDE (DSM-III-R) | 1 year after treatment | 71<br>66 | 43.7<br>57.6 |

ADM, Antidepressant medication; ADMI, antidepressant medication increase; CBT, cognitive behavior therapy; CT, cognitive therapy; CM, clinical management; MBCT, mindfulness-based cognitive therapy; MDE, major depressive episode; MM, medication management; RDC, Spitzer's Research Diagnostic Criteria; RR, risk ratio; TAU, treatment as usual; WBT, well-being therapy.

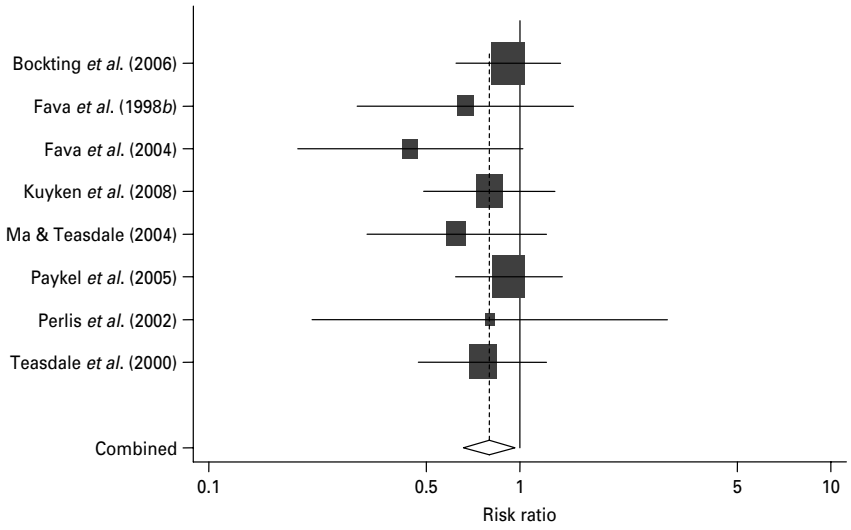


**Fig. 1.** Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder.

(95% CI 0.674–1.051) in the random-effects model. Neither $Q$ nor $I^2$ statistics suggested any significant heterogeneity among the studies pooled ($Q=1.359$, df = 4, $p=0.851$, $I^2=0\%$). Neither Begg's funnel plot nor Egger's test ($p=0.336$) indicated the presence of publication bias.

### *Sequential use of psychotherapy after discontinuation of antidepressant medication*

Only three studies contributed data (Fava *et al*. 1998*b*, 2004; Kuyken *et al*. 2008). Subgroup analysis showed that patients randomized to continuation-phase psychotherapy while antidepressant drugs were discontinued were significantly less likely to experience relapse/recurrence compared to other active (i.e. continuation of antidepressant medication) or non-active (i.e. CM) control conditions. Across the trials, the pooled RR for relapse was 0.650 (95% CI 0.463–0.912) in the random-effects model. The $Q$ statistic was not significant ($Q=4.171$, df = 2, $p=0.124$), even though the $I^2$ statistic indicated moderate variability in the treatment effects among the included studies ($I^2=52\%$). Neither visual inspection of Begg's funnel plot nor Egger's test ($p=0.359$) was suggestive for the presence of publication bias.

## Conclusions

In the present meta-analysis we found evidence that the sequential administration of psychotherapy (alone or in combination with antidepressant medication) after response to acute-phase pharmacotherapy may have a protective effect against relapse or recurrence in MDD, providing superior outcomes to control conditions. This can be seen as support for the hypothesis that psychotherapy generates skills that patients can continue to use after treatment ends to manage their own affective states, reducing internal and external risks for relapse or recurrence. Comparable learning may not take place with pharmacotherapy alone (Pava *et al*. 1994; Segal *et al*. 2003; Vittengl *et al*. 2007). In addition, the preventive effects of the sequential strategy seem to be related to an abatement of residual symptoms and/or an increase in psychological well-being and coping skills (Paykel *et al*. 1995; Fava *et al*. 1999; Rafanelli *et al*. 1999; Teasdale *et al*. 2002; Petersen *et al*. 2004).

Modifications of cognitive behavioral techniques (including MBCT, CBT of residual symptoms and WBT) were found to be as effective in reducing relapse/recurrence as standard CBT. This finding suggests that specific psychotherapeutic strategies directed toward dysfunctional cognitions and the affective response to these cognitions, in addition to those aimed at enhancing well-being in the residual phase of depressive disorders, may yield long-term benefits. Focus on this area of research has led to the development of psychotherapeutic strategies to address the unique needs of a patient who has already received acute-phase treatment.

A sequential strategy may include discontinuation of antidepressant drug treatment or its maintenance, thereby offering the advantage of yielding enduring effects while limiting exposure to drug therapy. The continuation of antidepressant medication during psychotherapy did not seem to be significantly more efficacious than tapering and discontinuation in this meta-analysis. However, the advantages of continuing medication during psychotherapy *versus* tapering and discontinuation have not been compared directly in a controlled study.

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In our investigation we found a non-significant trend favoring the combination of psychotherapy and antidepressant medication during the continuation phase compared to antidepressant medication alone. Instead, the sequential use of psychotherapy after discontinuation of antidepressant medication was found to be significantly more effective in reducing relapse/recurrence compared to control conditions. These results indicate that switching patients from one treatment (i.e. pharmacotherapy) to another (i.e. psychotherapy), after an adequate response to the first, may help to prevent relapse or recurrence. The effects of this strategy have been observed in lower relapse rates with the addition of psychotherapy than without, after the discontinuation of successful pharmacotherapy (Fava *et al*. 1998*b*, 2004). Thus evidence suggests that discontinuation of antidepressant drugs may be feasible when psychotherapy is provided. This is important in view of the fact that a substantial proportion of patients discontinue antidepressant therapy after responding to the initial acute-phase treatment, regardless of the physician's advice (Fava *et al*. 2003). Furthermore, loss of clinical effect of antidepressant drug treatment, despite adequate compliance, has also emerged as a clinical problem (Fabbri *et al*. 2007). However, the number of studies that contributed data for this subgroup analysis was too small and the $I^2$ statistic was indicative of moderate heterogeneity across the trials. Therefore, this finding has to be considered with caution. Further work is needed to find ways of extending care across multiple phases of MDD. The need for effective relapse-prevention strategies to treat the large number of patients for whom antidepressants are the first or only treatment received must be considered. It will also be important to evaluate both the longitudinal efficacy and cost-effectiveness of sequenced treatment protocols where specific and distinct interventions are provided to get patients well and then teach them how to stay that way. Thus, two important aspects of the sequential strategy need to be addressed. The first is that patients need to be motivated to undergo short-term psychotherapeutic treatment while they are apparently well. The other is that, whereas the other strategies may be undertaken with a non-specialist physician, implementation of the sequential approach requires referral to a specialized psychotherapist (Fava *et al*. 2003; Marks, 2009).

This meta-analysis has several limitations. First, the number of included studies, and also the sample sizes, were too small to allow any definite conclusions to be drawn. Second, the duration of treatments and the length of follow-up periods varied across the studies. Nevertheless, meta-regression analyses did not show significant effects on relapse/recurrence rates. Third, the use of control conditions (CM or TAU) also varied across the studies (Mohr *et al*. 2009). Fourth, no controlled studies have directly compared the use of psychotherapy during antidepressant continuation with tapering and discontinuation. Finally, all the included studies were related to cognitive-behavioral treatments because we could not find any single randomized controlled trial of the sequential use of other well-established psychotherapies, such as interpersonal psychotherapy (IPT), after response to pharmacotherapy. Therefore, the results should be interpreted with caution and need to be confirmed by subsequent clinical trials.

Despite these limitations, our findings lend support to the view that the sequential administration of psychotherapy after response to acute-phase pharmacotherapy, either alone or in combination with antidepressant drugs, may play a role in reducing relapse and recurrence in MDD. Because incomplete recovery from the first lifetime major depressive episode was found to predict a chronic course of illness during a 12-year prospective naturalistic follow-up (Judd *et al*. 2000), this approach seems to be particularly indicated whenever substantial residual symptoms are present.

The sequential model that was originally developed for preventing relapse and recurrence in MDD (Fava *et al*. 1994, 1996, 1998*b*) has also been applied to other psychiatric conditions, such as anxiety disorders (Fava *et al*. 1998*a*, 2005*a*), bipolar disorder (Scott *et al*. 2007; Williams *et al*. 2008) and chronic insomnia (Vallières *et al*. 2005; Morin *et al*. 2009), with promising results. Moreover, various studies have demonstrated that exposure-based behavioral therapy may yield long-term benefits to the majority of patients suffering from panic disorder with agoraphobia (Fava *et al*. 2001*b*), social phobia (Fava *et al*. 2001*a*), and generalized anxiety disorder (Fava *et al*. 1998*a*, 2005*b*), and allow tapering and discontinuation of psychotropic drugs in the course of treatment. The model is thus pragmatic, that is realistic instead of idealistic, in keeping with the complexity of the balance of positive and negative affects in health and disease (Fava *et al*. 2007; Bech, 2009) and the clinical needs of patients with affective disorders (Segal *et al*. 2003).

## Declaration of Interest

M. Fava has received research support from Abbott Laboratories, Alkermes, Aspect Medical Systems, AstraZeneca, Bio Research, BrainCells Inc., Bristol-Myers Squibb Company, Cephalon, Clinical Trial Solutions, Eli Lilly & Company, Forest Pharmaceuticals Inc., Ganeden, GlaxoSmithKline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, NARSAD, NCCAM, NIDA, NIMH,

Novartis, Organon Inc., PamLab, LLC, Pfizer Inc., Pharmavite, Roche, Sanofi-Aventis, Shire, Solvay Pharmaceuticals Inc., Synthelabo, and Wyeth-Ayerst Laboratories; has served on advisory boards for and has been a consultant to Abbott Laboratories, Amarin, Aspect Medical Systems, Astra-Zeneca, Auspex Pharmaceuticals, Bayer AG, Best Practice Project Management Inc., Biovail Pharmaceuticals Inc., BrainCells Inc., Bristol-Myers Squibb Company, Cephalon, Clinical Trials Solutions, CNS Response, Compellis, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eli Lilly & Company, EPIX Pharmaceuticals, Fabre-Kramer Pharmaceuticals Inc., Forest Pharmaceuticals Inc., GlaxoSmithKline, Grunenthal GmBH, Janssen Pharmaceuticals, Jazz Pharmaceuticals, J & J Pharmaceuticals, Knoll Pharmaceutical Company, Labopharm, Lorex Pharmaceuticals, Lundbeck, MedAvante Inc., Merck, Methylation Sciences, Neuronetics, Novartis, Nutrition 21, Organon Inc., PamLab LLC, Pfizer Inc., PharmaStar, Pharmavite, Precision Human Biolaboratory, Roche, Sanofi-Aventis, Sepracor, Schering-Plough, Solvay Pharmaceuticals Inc., Somaxon, Somerset Pharmaceuticals, Synthelabo, Takeda, Tetragenex, Transcept Pharmaceuticals, Vanda Pharmaceuticals Inc., and Wyeth-Ayerst Laboratories; has served on speakers' boards for Advanced Meeting Partners, American Psychiatric Association, AstraZeneca, Belvoir, Boehringer-Ingelheim, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithKline, Imedex, Novartis, Organon Inc., Pfizer Inc., PharmaStar, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed-Elsevier, UBC, Wyeth-Ayerst Laboratories; has equity holdings in Compellis; has patent applications for SPCD and for a combination of azapirones and bupropion in MDD; and receives copyright royalties for the MGH Cognitive and Physical Functioning Questionnaire, Sexual Functioning Inventory, Antidepressant Treatment Response Questionnaire, Discontinuation-Emergent Signs and Symptoms, and SAFER.

G. I. Papakostas has served as a consultant for AstraZeneca PLC, Bristol-Myers Squibb Company, Eli Lilly & Company, GlaxoSmithKline, Evotec AG, Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer Inc., Pierre Fabre Laboratories, Shire Pharmaceuticals, and Wyeth Inc.; has received honoraria from AstraZeneca PLC, Bristol-Myers Squibb Company, Eli Lilly & Company, Evotec AG, GlaxoSmithKline, Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, Lundbeck, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer, Pierre Fabre Laboratories, Shire Pharmaceuticals, Titan Pharmaceuticals, and Wyeth Inc.; has received research support from Bristol-Myers Squibb Company, Forest Pharmaceuticals, the National Institute of Mental Health, PAMLAB LLC, Pfizer Inc., and Precision Human Biolaboratories; and has served on the speakers' bureau for Bristol-Myers Squibb Company, and Pfizer Inc.

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