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Sequential Combination of Pharmacotherapy and Psychotherapy in Major Depressive Disorder
A Systematic Review and Meta-analysis

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IMPORTANCE The sequential model emerged from the awareness that the persistence of residual symptoms and the frequent occurrence of psychiatric comorbidity were both associated with poor long-term outcome of major depressive disorder (MDD).

OBJECTIVE To conduct an updated meta-analysis to examine the association of the sequential combination of pharmacotherapy and psychotherapy with reduced risk of relapse and recurrence in MDD.

DATA SOURCES Keyword searches were conducted in PubMed, PsycInfo, Web of Science, and the Cochrane Library from inception of each database through November 2019. Reference lists from relevant studies were examined using the following keywords: *sequential treatment*, *drugs and psychotherapy*, *combined treatment*, *continuation or maintenance*, *relapse or recurrence and prevention*, and *depress* or major depress**, selecting *adults* and *randomized controlled trials* as additional limits. Authors of selected articles were contacted if needed.

STUDY SELECTION Randomized clinical trials examining the effectiveness of the sequential use of psychotherapy following response to acute-phase pharmacotherapy in the treatment of adult remitted patients with MDD were selected independently by 2 reviewers.

DATA EXTRACTION AND SYNTHESIS The methods used fulfilled the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. Data extraction and methodologic quality assessment were conducted independently by the reviewers. Examination of the pooled results was performed based on the random-effects model. Heterogeneity between study results and likelihood of significant publication bias were assessed. Sensitivity analyses and meta-regressions were also run.

MAIN OUTCOMES AND MEASURES The primary outcome measures were relapse or recurrence rates of MDD, as defined by study investigators, at the longest available follow-up.

RESULTS Seventeen randomized clinical trials met criteria for inclusion in the meta-analysis, with 1 study yielding 2 comparisons (2283 patients overall, with 1208 patients in a sequential treatment arm and 1075 in a control arm). The pooled risk ratio for relapse/recurrence of MDD was 0.84 (95% CI, 0.74-0.94), suggesting a relative advantage in preventing relapse/recurrence for the sequential combination of treatments compared with control conditions.

CONCLUSIONS AND RELEVANCE The results of this systematic review and meta-analysis indicate that the sequential integration of psychotherapy following response to acute-phase pharmacotherapy, alone or combined with antidepressant medication, was associated with reduced risk of relapse and recurrence in MDD. The preventive value of the sequential strategy relies on abatement of residual symptoms and/or increase in psychological well-being. The steps for implementing the sequential approach in remitted patients with recurrent MDD are provided.

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The sequential model consists in the consecutive application of 2 forms of treatment, psychotherapy after pharmacotherapy and pharmacotherapy after psychotherapy, and sequential use of 2 psychotherapeutic or pharmacological strategies.[1] The sequential model does not fall within the realm of maintenance strategies, which have the aim of prolonging clinical responses that therapies have obtained,[2] nor of augmentation or switching strategies because of lack of response to the first line of treatment.[3] It is an intensive, 2-stage approach that derives from the awareness that 1 course of treatment with a specific tool (whether pharmacotherapy or psychotherapy) is unlikely to entail solutions to the affective disturbances of patients, both in research and clinical practice settings.[1] The rationale of this approach is to use psychotherapeutic strategies when they are most likely to make a unique and separate contribution to a patient's well-being and to achieve a more pervasive recovery.[1] The model emerged from 2 converging insights that developed in the 1990s.

One line of evidence derived from the growing awareness that residual symptoms, despite a successful response to acute-phase treatment, are frequently encountered after completion of drug or psychotherapeutic treatment in depression and were correlated with poor long-term outcome.[4-6] These findings have led to the hypothesis that residual symptoms at the end of treatment may progress to become prodromal symptoms of relapse and that treatment directed toward residual symptoms may yield long-term benefits.[4,7] Subsequent research in the past 2 decades has confirmed the importance of residual symptomatology.[8-10]

A complementary line of evidence suggested the frequent occurrence of other comorbid psychiatric disorders, particularly anxiety disorders, in major depression. Comorbidity may negatively affect longitudinal course and treatment outcome.[11-13] Thus, it is unlikely that 1 course of treatment may entail a solution to such complex clinical presentations.

Administration of psychotherapy after a successful course of pharmacotherapy was analyzed according to meta-analytic methods in a preliminary analysis in 2011[14] and in a subsequent update in 2016.[15] Both provided support to the sequential integration of pharmacotherapy and psychotherapy according to the stages of major depressive disorder (MDD) as an effective treatment strategy for preventing relapse and recurrence. Conversely, other reviews examining the combination of pharmacotherapy and psychotherapy regardless of the time of application and study design yielded mixed results.[16-21]

Since a number of additional randomized clinical trials (RCTs) applying the sequential model have been published after our last systematic review in 2016,[15] we conducted an updated meta-analysis to examine the association of the sequential administration of psychotherapy after successful response to acute-phase pharmacotherapy with reduced risk of relapse and recurrence in adult patients with MDD.

Key Points

Question Can the sequential combination of pharmacotherapy and psychotherapy reduce the risk of relapse and recurrence in patients with major depressive disorder?

Findings This systematic review and meta-analysis included 17 randomized clinical trials of 2283 participants and showed that the sequential integration of psychotherapy following response to acute-phase pharmacotherapy, alone or combined with antidepressant medication, was associated with reduced risk of relapse and recurrence in major depressive disorder.

Meaning The sequential model introduces a conceptual shift in clinical practice, and discontinuation of antidepressant drugs may be feasible when a sequential treatment model is used.

Methods

The methods used fulfilled the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[22] Published articles were identified with the use of electronic database searches. Searches were conducted in PubMed, PsycInfo, Web of Science, and the Cochrane Library from inception of each database through November 2019, using the following keywords: *sequential treatment*, *drugs and psychotherapy*, *combined treatment*, *continuation or maintenance*, *relapse or recurrence and prevention*, and *depress* or major depress**, selecting *adults* and *randomized controlled trials* as additional limits. References from relevant studies and reviews were checked for other RCTs not yet identified. Experts in the field and authors of significant articles were contacted if needed.

Studies were selected independently by 2 reviewers (J.G. and G.A.F.) and any disagreement was resolved by discussion. We selected RCTs examining the effectiveness of the sequential use of psychotherapy after response to acute-phase pharmacotherapy in adult (at least partially) patients with remitted MDD. Relapse or recurrence rates of depression, as defined by study investigators (ie, reaching a cutoff on any rating scale for depression used by authors and/or the occurrence of a defined major depressive episode after remission/recovery), at the longest available follow-up were considered as the primary outcome measures.

Studies that were not RCTs, did not contain original data, or did not primarily involve face-to-face psychotherapy were excluded. We also did not consider studies in which relapse or recurrence rates were not identified as binary outcomes. We excluded RCTs of continuation and maintenance treatments in which psychotherapy was also administered during the acute phase of MDD, so that continuation-phase treatment modalities matched those used during the initial phase.

We excluded studies that involved patients younger than 18 years or older than 65 years at the first onset of depression; involved pregnant individuals only; exclusively focused on the treatment of patients with bipolar disorder, dysthymic disorder, minor depressive disorder, or seasonal affective disorder; or included 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.

Finally, studies that were judged to be dissimilar from other investigations on the basis of clinical characteristics of the intervention, such as use of electroconvulsive therapy in addition to antidepressant treatment[23] and telephone- or internet-based psychotherapy,[24-29] were excluded, as suggested by Jane-Wit et al[30] and Concato and Horwitz.[31]

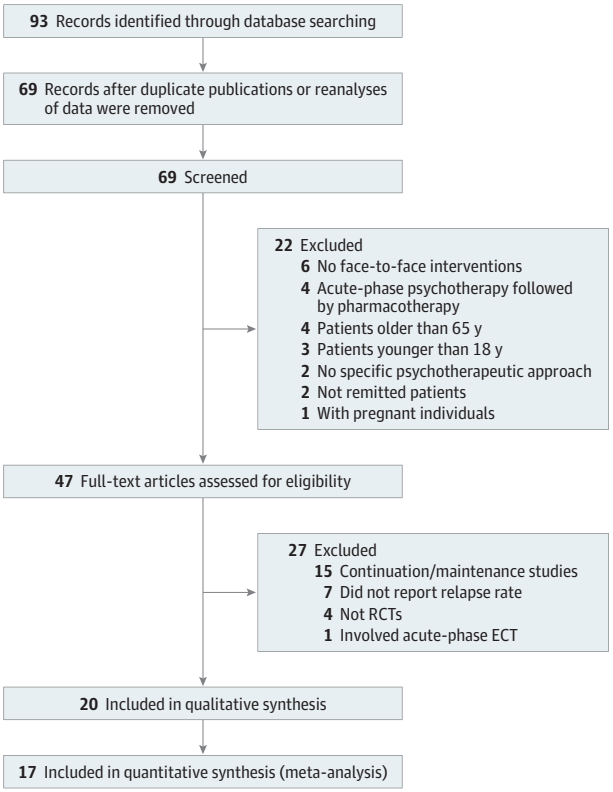
Both reviewers extracted data independently with the use of a precoded form. The following information were extracted from studies included in the meta-analysis: age, sex, methods used to assess study participants, and other inclusion criteria (ie, recovered from a major depressive episode or in remission); type of psychotherapeutic intervention or control condition; number of patients randomly assigned to each treatment arm; length of treatment and assessment times; and relapse/recurrence definitions and rates. Both reviewers independently assessed the methodologic quality of the included trials based on 3 key domains: random allocation of treatments, blinding of outcome assessment, and handling of attrition.

Relapse/recurrence rates were considered as the primary outcome of the meta-analysis. Therefore, the risk ratio (RR) of relapse or recurrence and its standard error were computed from each included study. The pooled results were examined based on the random-effects model to increase the generalizability of findings since this model is more conservative compared with the fixed-effects model. An α level of .05 was considered for hypothesis tests.

In addition to point estimates and confidence intervals, the *Q* statistic was run to assess heterogeneity between study results, testing for the null hypothesis that effect sizes from each of the studies were similar enough that a common population effect size could be computed.[32] However, this statistic only informs about the presence of heterogeneity, and it does not provide information on the extent of such heterogeneity. The I^2 statistic, which displays heterogeneity in percentages, was also calculated. Values ranging from 0% to 40% indicate no observed heterogeneity, and larger values show increasing heterogeneity, with 30% to 60% as moderate, 50% to 90% as substantial, and 75% and higher as considerable heterogeneity.[33]

The likelihood of significant publication bias was assessed through funnel plot[33] and testing for asymmetry using the Egger test statistic.[34] The Duval and Tweedy trim-and-fill procedure was also performed.[35] 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 outcome changed. Meta-regression was conducted to investigate how certain characteristics (ie, drug continuation during psychotherapy, treatment duration, and length of follow-up) acted to influence treatment outcomes. Finally, clinical heterogeneity between studies was explored performing subgroup analyses. All analyses were performed using the user-written packages for meta-analysis available in Stata version 10.1 (StataCorp). Analysis began January 2020.

Figure 1. Flowchart of Included Studies



ECT indicates electroconvulsive therapy; RCT, randomized clinical trial.

Results

Characteristics of Included Studies

The initial search strategies yielded 93 articles for potential inclusion in the meta-analysis (**Figure 1**). Of these, 17 studies[36-52] met criteria for inclusion in the meta-analysis, with 1 study[51] yielding 2 comparisons. Five additional RCTs were included in the present meta-analysis compared with the 2016 meta-analysis.[15] These studies reported relapse and/or recurrence rates for a total of 2283 participants (1208 patients in a sequential treatment arm and 1075 in a control arm). The mean (SD) age of participants was 45.9 (2.9) years, and 69.2% (range, 49.5%-81%) were female. They were judged as fully or partially remitted after acute-phase pharmacotherapy, based on clinical interviewing. Characteristics of the RCTs included in the meta-analysis are presented in the **Table**. All studies involved cognitive behavior therapy and its modifications (ie, preventive cognitive therapy, cognitive behavioral therapy of residual symptoms, well-being therapy, mindfulness-based cognitive therapy). Treatment was delivered in a group format in 12 studies,[37,40,42-45,47-52] whereas individual sessions were used in 5 studies.[36,38,39,41,46] Six studies compared a sequential treatment arm with antidepressant medication

Table. Selected Characteristics of Included Studies

Source	Age, mean (SD), y	Female, %	Relevant treatment conditions	Treatment duration, wk	Relapse or recurrence definition	Length of follow-up	No. of participants	Rates of relapse or recurrence, %
Bockting et al,[48] 2015	44.7 (9.5)	74	PCT and TAU	8	MDE (*DSM-IV*)	10 y After randomization	88	87
			TAU				84	94
Bockting et al,[51] 2018[a]	47.3 (10.3)	65	PCT and ADM	8	MDE (*DSM-IV*)	24 mo After randomization	104	42
			PCT and tADM				85	64
			ADM				100	60
Bondolfi et al,[43] 2010	47.5 (NA)	72	MBCT and TAU	8	MDE (*DSM-IV*)	14 mo After treatment	31	29
			TAU				29	35
Fava et al,[36] 1998[a]	43.7 (2.3)	68	CBT of residual symptoms	20	MDE (RDC)	6 y After treatment	20	50
			CM				20	75
Fava et al,[39] 2004[a]	46.9 (11.2)	60	CBT of residual symptoms and WBT	20	MDE (RDC)	6 y After treatment	20	40
			CM				20	90
Godfrin and van Heeringen,[44] 2010	45.7 (10.6)	81	MBCT and TAU	8	MDE (*DSM-IV-TR*)	14 mo After randomization	40	30
			TAU				47	68
Huijbers et al,[49] 2015	51.7 (14.3)	72	MBCT and ADM	8	MDE (*DSM-IV*)	13 mo After treatment	33	36
			ADM				35	37
Kuyken et al,[42] 2008[a]	49.2 (11.2)	76	MBCT	8	MDE (*DSM-IV*)	15 mo After randomization	61	48
			ADM				62	60
Kuyken et al,[50] 2015[a]	49.5 (12.5)	77	MBCT	8	MDE (*DSM-IV*)	24 mo After randomization	212	44
			ADM				212	47
Ma and Teasdale,[40] 2004	44.5 (8.9)	76	MBCT and TAU	8	MDE (*DSM-IV*)	1 y After treatment	36	39
			TAU				37	62
Paykel et al,[41] 2005	43.4 (10.5)	50	CBT, ADM, and CM	20	MDE (*DSM-III-R*)	6 y After randomization	80	60
			ADM and CM				78	65
Perlis et al,[38] 2002	39.9 (10.3)	55	CT and ADMI	26	MDE (*DSM-IV*)	7 mo After randomization	66	6
			MM and ADMI				66	8
Segal et al,[45] 2010[a]	44 (11)	63	MBCT	8	MDE (*DSM-IV*)	18 mo After randomization	26	39
			CM				30	60
Shallcross et al,[52] 2018	34.8 (11.2)	76	MBCT and TAU	8	MDE (*DSM-V*)	26 mo After treatment	46	48
			ACC and TAU				46	50
Stangier et al,[46] 2013	48.6 (11.6)	72	CBT, MBCT, WBT, and TAU	32	MDE (*DSM-IV*)	1 y After randomization	90	51
			Psychoeducation and TAU				90	60
Teasdale et al,[37] 2000	43.5 (9.9)	76	MBCT and TAU	8	MDE (*DSM-III-R*)	1 y After treatment	71	44
			TAU				66	58
Williams et al,[47] 2014	43.8 (11.79)	70	MBCT and TAU	8	MDE (*DSM-IV*)	1 y After treatment	99	46
			TAU				53	53

Abbreviations: ACC, active control condition; ADM, antidepressant medication; ADMI, antidepressant medication increase; CBT, cognitive behavioral therapy; CM, clinical management; CT, cognitive therapy; MBCT, mindfulness-based cognitive therapy; MDE, major depressive episode; MM, medication management; NA, not applicable; PCT, preventive cognitive therapy; RDC, Research Diagnostic Criteria; tADM, tapering of antidepressant medication; TAU, treatment as usual; WBT, well-being therapy.

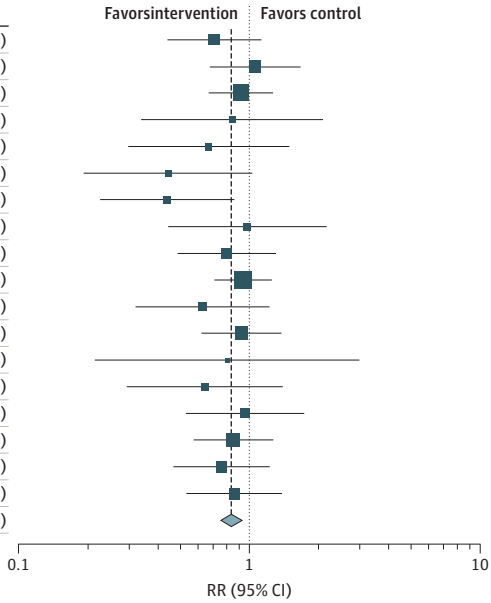
[a] Studies involving drug discontinuation.

(ADM) and clinical management,[38,41,42,49-51] 6 with treatment as usual alone,[37,40,43,44,47,48] 2 with treatment as usual combined with active control condition[52] or psychoeducation,[46] and 3 with clinical management alone.[36,39,45] Treatment as usual involved standard care as typically provided by the referring agencies (eg, primary care physicians or other sources), with no restriction on the use of pharmacotherapy. Clinical management consisted of monitoring drug administration (including tapering ADM), reviewing the patient's clinical status, and providing limited support and advice when needed, whereas specific treatment ingredients (eg, exposure strategies, diary work, cognitive restructuring) were proscribed. Active control condition was designed as an active control group for mindfulness-based interventions, including physical activity, functional movement, music therapy, and nutrition but lacking any mindfulness element. Psychoeducation was intended to improve the clinical management of psychiatric

Figure 2. Sequential Combination of Pharmacotherapy and Psychotherapy Associated With Reduced Relapse/Recurrence Risk in Major Depressive Disorder

Source	RR (95% CI)
Bockting et al,[51] 2018	0.70 (0.44-1.12)
Bockting et al,[51] 2018[a]	1.06 (0.68-1.65)
Bockting et al,[48] 2015	0.92 (0.67-1.26)
Bondolfi et al,[43] 2010	0.84 (0.34-2.07)
Fava et al,[36] 1998[a]	0.67 (0.30-1.48)
Fava et al,[39] 2004[a]	0.44 (0.19-1.02)
Godfrin and van Heeringen et al,[44] 2010	0.44 (0.23-0.86)
Huijbers et al,[49] 2015	0.98 (0.45-2.15)
Kuyken et al,[42] 2008[a]	0.80 (0.49-1.30)
Kuyken et al,[50] 2015[a]	0.94 (0.71-1.25)
Ma and Teasdale et al,[40] 2004	0.63 (0.32-1.22)
Paykel et al,[41] 2005	0.92 (0.62-1.37)
Perlis et al,[38] 2002	0.80 (0.21-2.98)
Segal et al,[45] 2010[a]	0.64 (0.30-1.39)
Shallcross et al,[52] 2018	0.96 (0.53-1.72)
Stangier et al,[46] 2013	0.85 (0.58-1.26)
Teasdale et al,[37] 2000	0.76 (0.47-1.22)
Williams et al,[47] 2014	0.86 (0.54-1.38)
Total	0.83 (0.74-0.94)

Heterogeneity: $\chi^2_{17} = 10.71$; $P = .87$; $I^2 = 0\%$
Test for overall effect: $z = -3.05$; $P = .002$



RR indicates risk ratio.
[a] Studies involving drug discontinuation.

care and focused mainly on education and information, without using any specific psychotherapeutic techniques.

The methodological quality of the included RCTs was high. In all studies, participants were randomly assigned to the conditions, and assessors were blinded to patients' treatment allocation. Intention-to-treat analyses were implemented in 14 studies,[37,38,40-46,48-52] while all patients were retained in 2 studies,[36,39] and 1 study reported completers' data only.[47]

Sequential Integration of Psychotherapy and Pharmacotherapy

We compared the outcomes of the sequential integration of psychotherapy (either alone or in combined with ADM) with control conditions (**Figure 2**). The pooled RR for relapse/recurrence was 0.835 (95% CI, 0.743-0.938) in the random-effects model, indicating a relative advantage in preventing relapse/recurrence (ie, lower risk of relapse/recurrence) for the sequential approach compared with active and nonactive controls. We did not find significant heterogeneity among the pooled studies ($Q = 10.713$; $df = 17$; $P = .87$). The I^2 statistic also indicated no observed heterogeneity ($I^2 = 0\%$) across trials. Both visual inspection of funnel plot and Egger test ($P = .02$) were suggestive for the presence of publication bias. When implementing the trim-and-fill method, the adjusted effectiveness of the sequential approach remained significant (RR = 0.885; 95% CI, 0.793-0.988). A sensitivity analysis was performed to examine the contribution of each study to the overall effect size, and none of them appeared to markedly influence the observed RR for relapse or recurrence.

Meta-regression analyses did not indicate any advantage of continuing medication during psychotherapy vs tapering and discontinuation (coefficient, −0.023; 95% CI, −0.144 to 0.097). We also tested for treatment duration as well as for the length of follow-up, and no significant associations with relapse/recurrence rates were found among the included studies (coefficient, −0.020; 95% CI, −0.160 to 0.120 and coefficient, 0.021; 95% CI, −0.639 to 0.681, respectively).

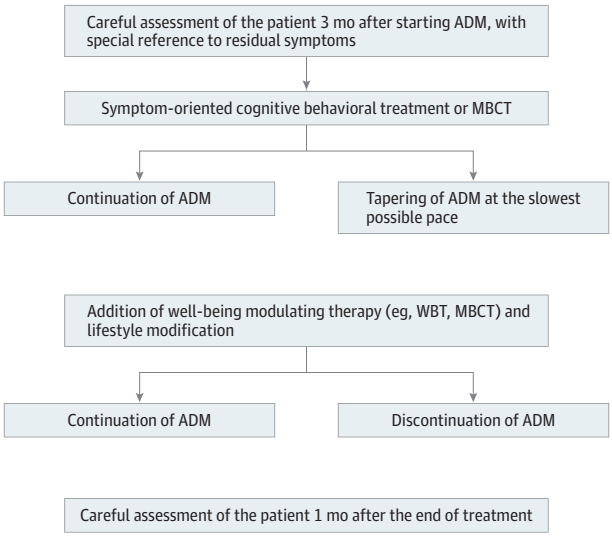
Sequential Use of Psychotherapy During Continuation of ADM

Studies involving the sequential use of psychotherapy during continuation of antidepressant drugs and those with tapering and discontinuation were examined separately. Twelve RCTs contributed data for this subgroup analysis.[37,38,40,41,43,44,46-49,51,52] Data displayed a significant difference in favor of the administration of psychotherapy during continuation of ADM in reducing rates of relapse/recurrence compared with active control conditions (ie, continuation of ADM) or treatment as usual. The pooled RR for relapse was 0.821 (95% CI, 0.710-0.949) in the random-effects model. Both Q and I^2 statistics were not suggestive of any significant heterogeneity among the pooled studies ($Q = 5.900$; $df = 11$; $P = .88$; $I^2 = 0\%$). Inspection of funnel plot and Egger test ($P = .27$) did not indicate the presence of publication bias.

Sequential Use of Psychotherapy After Discontinuation of ADM

Six studies contributed data.[36,39,42,45,50,51] Subgroup analysis indicated that patients randomized to continuation-phase psychotherapy after discontinuation of ADM were not more likely to experience relapse/recurrence compared with either nonactive (ie, clinical management) or active control con-

Figure 3. Steps for Implementing the Sequential Approach in Patients With Recurrent Depression



ADM indicates antidepressant medication; MBCT, mindfulness-based cognitive therapy; WBT, well-being therapy.

ditions (ie, continuation of ADM). Across the trials, the pooled RR for relapse was 0.860 (95% CI, 0.708-1.044) in the random-effects model. The *Q* statistic was not significant ($Q = 4.670$; $df = 5$; $P = .46$), as well as the I^2 statistic ($I^2 = 0\%$). Both visual inspection of funnel plot and Egger test ($P = .049$) were suggestive for the presence of publication bias.

Discussion

The chronic and recurrent nature of MDD represents a major clinical challenge. Prevention of relapse and recurrence appears to be a crucial task for successful treatment. Clinical guidelines[53,54] tend to recommend long-term treatment with ADM for relapse prevention and additional psychotherapy for patients with depression who are at significant risk of relapse, such as those with more previous depressive episodes or who still have residual symptoms. The results of this updated systematic review and meta-analysis indicate that the sequential administration of psychotherapy after response to acute-phase pharmacotherapy, either alone or in combination with ADM, was associated with reduced risk of relapse and recurrence in MDD.

This provides support to the hypothesis that psychotherapy may generate skills that patients can continue to practice after treatment ends to regulate their own affective states, reducing both internal and external triggers for relapse or recurrence. Comparable learning may not take place with pharmacotherapy alone.[55] Further, the preventive value of the sequential strategy appears to be related to abatement of residual symptoms[9] and/or increase in psychological well-being.[56]

The application of the psychotherapeutic intervention in the sequential model departs from the traditional treatment strategies in depression and, despite differences in characteristics of interventions, has some common features. First, it is applied to the residual phase of MDD according to a longitudinal view of development of disorders that can be subsumed under the staging model.[9,57,58] Second, the target of psychotherapeutic work is no longer predetermined but varies according to the nature, characteristics, and intensity of residual symptoms[1,59] based on an individualized treatment plan. A clinimetric characterization encompasses repeated assessments, macroanalysis and microanalysis, and identification of disorders as transfer stations (instead of diagnostic endpoints), which are amenable to longitudinal verification and modification as long as therapeutic goals are achieved.[1,59] Third, the studies that used a sequential approach in the treatment of MDD clearly indicated that the level of remission obtained by successful acute-phase pharmacotherapy could be increased by a subsequent psychotherapeutic treatment.[60] Indeed, a full recovery can be reached only through interventions that facilitate progress toward restoration or enhancement of psychological well-being.[56] Finally, all the included studies involved variations of cognitive-behavioral treatments. In a few cases[36,39,46] they were integrated with well-being therapy[61] or some ingredients of well-being therapy.[51] Indeed, the addition of well-being–modulating psychotherapeutic strategies appears to be an increasingly recognized step to the pursuit of euthymia.[56]

A sequential strategy may include maintenance of antidepressant drug treatment or its discontinuation. Thus, the sequential model offers a unique opportunity for antidepressant drug tapering and discontinuation, with the advantage of yielding enduring results while limiting exposure to ADM,[1] as was found to be the case in several investigations.[36,39,42,45,50,51] Withdrawal symptoms following discontinuation are common with any type of AD but particularly with selective serotonin reuptake inhibitors[62] and serotonin-norepinephrine reuptake inhibitors.[63] We have no way to know how many of the relapses were actually withdrawal in the groups that underwent drug tapering and discontinuation unless specific assessment strategies are endorsed, such as use of diagnostic criteria.[64] Thus, the number of relapses in the ADM tapering and discontinuation groups might have been overestimated.[65]

Discontinuation of ADM, such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, represents a major clinical challenge.[66] The sequential administration of psychotherapy in the residual phase allows to provide psychological support to the patient when withdrawal symptoms (despite slow tapering) do occur, and to regularly monitor the patient's clinical status over time. Indeed, the evidence suggests that discontinuation of ADM may be feasible when a sequential treatment model is used.[36,39,42,45,50,51]

The steps for implementing the sequential approach in remitted patients with recurrent depression have been described in detail.[59] An updated schema is provided in **Figure 3**. A careful assessment of the patient 3 months after starting ADM, with special reference to residual symptoms, should be the first step. The decision of whether prolonging pharmacotherapy or not should then be made. A second step is the

administration of a cognitive behavioral treatment of residual symptoms, which might include cognitive restructuring, homework exposure, and/or mindfulness-based cognitive therapy. If discontinuation of ADM is chosen, tapering should be performed at the slowest possible pace to minimize the risk of ADM withdrawal syndromes. In clinical practice, it may be necessary to extend the tapering phase and the performance of psychotherapy beyond the schedules used in RCTs. Psychotherapy may be divided in 2 parts: one is concerned with residual symptomatology, the other with well-being-modulating psychotherapeutic strategies.[56] These latter strategies are ideal for making the patient aware of a state of allostatic overload,[67] such as chronic and subtle life stresses, excessive workloads, and sleeping habits, with ensuing suggestions for lifestyle modification.[1] Finally, psychotherapy should be completed and the patient should be carefully assessed 1 month after the end of treatment.

Limitations

Findings from this updated meta-analysis should be interpreted with caution because of several limitations. First, the research designs that have been used varied substantially across studies and in some cases may have produced overly optimistic results. Approximately half of the studies compared the sequential approach with treatment as usual (where ADM treatment generally followed a naturalistic protocol), and any differences might have reflected nonspecific factors and expectations.[68] However, highly significant differences were also detected against clinical management that consisted of the same number and duration of sessions as the treatment condition.[36,39,45] When active control comparison groups were used, significant differences occurred in some studies, although to a lesser degree compared with other investigations, whereas did not in others.[38,49,50] Second, we could not include in the meta-analysis 3 RCTs using the sequential approach because of lack of a valid comparator.[69-71] Furthermore, the generalizability of findings might be affected also by study exclusion criteria, particularly as to the predominance of other comorbid conditions. Additional limitations are that the sample sizes, the duration of treatments, and the length of follow-up varied across trials. Nonetheless, meta-regression analyses did not show a significant association with relapse/recurrence rates. Only 1 of the included studies[51] directly compared the administration of psychotherapy during ADM continuation with ADM tapering and discontinuation. There is a need for additional RCTs comparing continuation and discontinuation of ADM during the use of psychotherapy in the residual phase of MDD, as well as head-to-head comparisons between different treatment strategies (ie, psychotherapy alone, pharmacotherapy alone, their simultaneous combination, or sequential integration).

Conclusions

The results of this updated systematic review and meta-analysis indicate that the sequential administration of psychotherapy after response to acute-phase pharmacotherapy, either alone or in combination with ADM, was associated with reduced risk of relapse and recurrence in MDD. The sequential model introduces a conceptual shift in clinical practice. The aim of the sequential approach is to add therapeutic ingredients for as long as they are needed. Therapeutic targets depend on the patient's response to the first course of treatment. It allows patients who are already receiving ADM to be randomized to alternative therapeutic options according to stages of development of depressive illness and not simply to cross-sectional diagnostic classification. Thus, the sequential integration of psychotherapy after successful administration of ADM during the acute phase of MDD appears to be an effective strategy that yields enduring results in the prevention of the vexing problems of relapse and recurrence.

ARTICLE INFORMATION

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Author Contributions: Drs Guidi and Fava had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Both authors.
Acquisition, analysis, or interpretation of data: Both authors.
Drafting of the manuscript: Both authors.
Critical revision of the manuscript for important intellectual content: Both authors.
Statistical analysis: Guidi.
Administrative, technical, or material support: Guidi.
Supervision: Both authors.

Conflict of Interest Disclosures: Dr Fava has written a book on well-being therapy, for which he receives no royalties. No other disclosures were reported.

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