Clinical Guidelines for the Treatment of Depressive Disorders

V. Combining Psychotherapy and Pharmacotherapy

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Background: The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments partnered to produce clinical guidelines for psychiatrists for the treatment of depressive disorders.

Methods: A standard guidelines development process was followed. Relevant literature was identified using a computerized Medline search supplemented by review of bibliographies. Operational criteria were used to rate the quality of scientific evidence, and the line of treatment recommendations included consensus clinical opinion. This section, “Combining Psychotherapy and Pharmacotherapy,” was 1 of 7 articles drafted and reviewed by clinicians. Revised drafts underwent national and international expert peer review.

Results: Recommendations are given for the use of combined psychotherapy and pharmacotherapy for the treatment of depressive disorders. Three methods of combined treatment are identified: concurrent treatment (psychotherapy plus pharmacotherapy) for the acute-treatment phase, sequential treatment (adding the other treatment for nonresponders or partial responders to monotherapy in the acute-treatment phase), and crossover treatment (switching to psychotherapy for the maintenance-treatment phase after response to pharmacotherapy in the acute phase).

Conclusions: Combined treatment with psychotherapy and pharmacotherapy is widely used in clinical practice. The recommendations for use of combined treatment are, however, based on only a limited evidence base.

INTRODUCTION

Specific psychotherapies and pharmacotherapy are effective treatments for depressive disorders (see Sections III and IV). There is little evidence, however, to guide a decision between monotherapy with either treatment. Hence, the choice of treatment rests on clinical assessment. Factors to consider in this choice include severity and chronicity of the depressive episode, responses to past treatments, potential side effects or relative contraindications to pharmacotherapy, availability of psychotherapy, and patient preference.

In addition to monotherapy, there is also the option to combine pharmacotherapy and psychotherapy. For many years, combined treatment was a time-honoured principle in the clinical practice of psychiatry (1). The potential benefits of combining psychotherapy and pharmacotherapy include improved treatment response, enhanced quality of life, reduced relapse/recurrence rates, and facilitation of lower medication dosages, along with enhanced compliance (2-5). The additional costs of combined treatment (not only economic costs, but also costs associated with side effects and time for treatment) may not, however, be justified if results are not clearly superior to those obtained with monotherapies (6).

Unfortunately, there are still very few studies evaluating combined treatment. This section reviews the limited evidence for combining psychotherapy with pharmacotherapy and gives clinical recommendations for the use of combined treatment.

1. What are the practical issues in providing combined treatment?

There are 2 main objectives in considering combination treatments: increasing response or remission rates (enhanced efficacy) during acute interventions, and reducing the rate of relapse or recurrence (relapse prevention) during maintenance treatments. Three methods of combined treatment have been systematically evaluated in a small number of controlled trials (see Table 5.1). While most of the earlier studies failed to demonstrate the “added value” of combination therapy for major depressive disorder (MDD), several subsequent, larger trials found that combined therapy conferred a significant advantage for chronic depression (2) and dysthymia (7). Different levels of chronicity and severity may partly explain the different conclusions across studies.

Combined treatment can be provided by a single individual, and in psychiatric practice this is probably the most common approach. Where a single treatment provider does not have the skills to perform the additional treatment, combined therapy would involve teamwork between a physician and a non-physician therapist or between 2 physicians. When a single clinician oversees the combined treatment, it is important to provide the patient with a rationale or overview of the way in which medications and psychological interventions are...
were treated to remission with a combination of IPT and A similar design was used to evaluate combined treatment for cant advantage over medication alone (12). had a modest effect; the combination did not produce significant prophylactic effect, while the maintenance IPT had a modest effect; the combination did not produce significant advantage over medication alone (12).

A similar design was used to evaluate combined treatment for maintenance treatment of elders with depression (3). Patients were treated to remission with a combination of IPT and nortriptyline and then randomized to 1 of 4 maintenance-treatment conditions: nortriptyline alone, placebo alone, placebo and monthly maintenance IPT, or nortriptyline and monthly maintenance IPT. Recurrence rates over 3 years were 20% for the combined nortriptyline plus IPT, compared with 43% for nortriptyline alone, 64% for IPT plus placebo, and 90% for placebo alone. Combined nortriptyline plus IPT was significantly superior to placebo plus IPT, but there was only a trend to superiority over nortriptyline monotherapy (P = 0.06).

In a very large RCT (n = 681), cognitive-behavioural analysis system of psychotherapy (CBASP) in combination with nefazodone was significantly more effective than either treatment alone in the acute treatment of chronic depression (2) (see also Section III). The response rates for CBASP, nefazodone, and the combination were 48%, 48%, and 73%, respectively, while remission rates were 33%, 29%, and 48%, respectively.

While patients or therapists in these RCTs were not masked, the use of blinded raters in most of these studies reduced the likelihood that the treatment effects for psychotherapy were inflated. Additionally, the fact that many of these studies also included placebo and clinical management (CM) conditions meant that there was a level of control for the effects of non-specific factors, such as attention and structure, associated with receiving treatment.

<table>
<thead>
<tr>
<th>Table 5.1 Methods of combined treatment</th>
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<tbody>
<tr>
<td>Combination design</td>
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<tr>
<td>Concurrent</td>
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<tr>
<td>Sequential</td>
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<tr>
<td>Crossover</td>
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2. How effective is combined concurrent treatment?

Most of the combined-treatment studies have involved concurrent treatment (2,3,9–19). The effectiveness of combined concurrent treatment was evaluated in a megaanalysis involving approximately 600 patients with unipolar depression who had received either 16 weeks of cognitive-behavioural therapy (CBT) alone, or interpersonal therapy (IPT) alone, or IPT plus antidepressants (19). Megaanalysis differs from metaanalysis in that it allows the data of each individual to be retained and permits testing for interactions between treatment types and patient characteristics. There were no significant differences among treatments in less severely ill patients. Remission rates (defined as a Hamilton Depression Rating Scale [HDRS] score of 7 or less for at least 4 weeks that was maintained until week 16) were 37% for IPT alone and 48% for combined treatment. For more severely ill patients, combination treatment involving IPT was significantly better than IPT alone (49% compared with 25%).

Unfortunately, the combination of CBT plus pharmacotherapy was not evaluated in the metaanalysis. However, 2 of 3 randomized controlled trials (RCTs) comparing CBT, pharmacotherapy, and the combination, did not find any differences among treatments in the acute treatment of MDD (11,14), while the third found that combination treatment was superior only to pharmacotherapy alone (9). Two of these studies reported relapse/recurrence rates in follow-up. CBT had lower relapse/recurrence rates than did pharmacotherapy alone; however, the combination treatment did as well as CBT alone (10,18).

The role of IPT and pharmacotherapy in maintenance treatment was also addressed in a 3-year RCT (12). Five treatments were compared: imipramine alone, placebo alone, maintenance IPT alone, maintenance IPT and placebo, and imipramine and maintenance IPT. Imipramine had a highly significant prophylactic effect, while the maintenance IPT had a modest effect; the combination did not produce significant advantage over medication alone (12).

A similar design was used to evaluate combined treatment for maintenance treatment of elders with depression (3). Patients were treated to remission with a combination of IPT and noradrenaline and then randomized to 1 of 4 maintenance-treatment conditions: nortriptyline alone, placebo alone, placebo and monthly maintenance IPT, or nortriptyline and monthly maintenance IPT. Recurrence rates over 3 years were 20% for the combined nortriptyline plus IPT, compared with 43% for nortriptyline alone, 64% for IPT plus placebo, and 90% for placebo alone. Combined nortriptyline plus IPT was significantly superior to placebo plus IPT, but there was only a trend to superiority over nortriptyline monotherapy (P = 0.06).

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### Recommendations for Concurrent Combined Treatment

#### Acute-phase treatment

Concurrent combined treatment is not recommended because there is no evidence for greater efficacy than that achieved with psychotherapy or pharmacotherapy alone (Level 2 evidence), except in the following circumstances:

- **First-line treatment**
  - Chronic depression: cognitive-behavioural analysis system of psychotherapy (CBASP) plus nefazodone is more effective than either treatment alone (Level 2 evidence).
  - Severe depression: interpersonal therapy (IPT) plus pharmacotherapy may be more effective than either treatment alone (Level 1 evidence).

#### Maintenance-phase treatment

Concurrent combined treatment is not recommended because there is no evidence for greater efficacy than that achieved with psychotherapy or pharmacotherapy alone (Level 2 evidence), except in the following circumstances:

- **First-line treatment**
  - Elderly patients: IPT plus nortriptyline may reduce relapse rates, compared with either treatment alone, in patients treated with the combination in the acute phase (Level 2 evidence).
psychotherapy or discontinue in favour of CM should also be considered (8).

One study addressed the question of adding medications to psychotherapy (IPT) nonresponders, compared with starting with both treatments combined. Two cohorts of women with recurrent MDD were treated with combination IPT and imipramine at the outset of treatment or with IPT alone, with sequential addition of imipramine for IPT nonresponders (13). Results showed that a significantly greater percentage of women treated sequentially achieved remission (79%), compared with women treated with concurrent combination therapy (66%). The strategy of first providing IPT to women with recurrent depression and then adding antidepressant medication if remission is not achieved may be especially relevant to women who are considering pregnancy and/or breastfeeding.

Conversely, the benefit of adding psychotherapy (CBT) to antidepressant medications was also demonstrated in a study of partially remitted patients (17). Patients continued to receive pharmacotherapy (primarily tricyclic antidepressants [TCAs] or selective serotonin reuptake inhibitors [SSRIs]) at the same dose and were randomized to receive CM or CBT. CBT significantly reduced relapse rates during a 1-year follow-up: 29% for CBT, compared with 47% with CM. This is one of the first randomized trials to show that the prevention of relapse by CBT has an additive effect with medication. Further, CBT was started after partial remission, avoiding the potential difficulties of a differential group composition as a function of treatments offered.

<table>
<thead>
<tr>
<th>Recommendations for Sequential Combined Treatments</th>
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<tbody>
<tr>
<td>There is limited evidence to support a sequential combined strategy: that is, adding psychotherapy or pharmacotherapy to patients who show nonresponse or partial response to monotherapy.</td>
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<tr>
<td>Second-line treatment</td>
</tr>
<tr>
<td>• Adding cognitive-behavioural therapy (CBT) for patients with residual depressive symptoms after acute treatment with pharmacotherapy improves remission rates and reduces relapse/recurrence rates (Level 2 evidence).</td>
</tr>
<tr>
<td>• Adding pharmacotherapy for women with partial or no response after acute treatment with interpersonal therapy (IPT) may improve remission rates (Level 3 evidence).</td>
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4. How effective is the crossover from pharmacotherapy in the acute phase to psychotherapy in the maintenance phase for the prevention of depressive relapse/recurrence?

It is now generally accepted that the long-term outcome for many patients with depression is disappointing. Substantial rates of relapse and recurrence have been reported in numerous follow-up studies. Some patients, even though they responded to medications in the acute phase of treatment, express a preference for nonpharmacologic treatments for maintenance treatment.

In an effort to address this problem, newer treatment strategies have been developed to capitalize on the efficacy of well-administered, specific treatments for different phases of depression. When combined, these multiple interventions may provide more long-term benefit to patients than do each of the treatments delivered on its own. The studies in this section are more concerned with increasing survival time to relapse/recurrence and are less focused on the nature of the acute-phase response. In fact, a full acute-phase response and remission is often required for patients to be eligible for crossover to the second treatment.

One such study assessed the efficacy of crossing over from acute treatment with various antidepressant medications to CBT for maintenance treatment (20). Subjects were stratified into 3 well-matched conditions: 1) treatment with antidepressant medication during acute treatment and follow-up; 2) antidepressant medication during the acute phase with CBT during follow-up; and 3) CBT during both acute phase and follow-up. Analysis of the 16-week acute phase revealed no significant differences across the 3 conditions, with all showing significant improvement. Over the 2-year follow-up period, there were no significant differences in relapse rates among the treatments.

The effect of modified cognitive-behavioural treatment (m-CBT) on residual symptoms, following successful pharmacotherapy, was also addressed in 2 small randomized studies (21,22). The m-CBT consisted of cognitive therapy (CT), lifestyle modifications, and well-being therapy. Forty patients with primary MDD were treated to remission with mainly TCA medications. Medications were tapered and eventually discontinued. Patients were assigned to either m-CBT or CM. There are 3 reports of patient outcomes assessed by longitudinal follow-up. At 2-year follow-up, there was no significant difference in relapse rates between m-CBT and CM (21), but at 4-year follow-up the m-CBT condition had significantly fewer relapses (35% relapse rate, compared with 70% for CM) (23). By the 6-year follow-up, there were again no significant differences between the 2 treatments. When multiple depressive relapses were considered, however, the CM group had significantly more depressive episodes than did the m-CBT group (24). In a similar study of recurrent MDD, m-CBT demonstrated a significant advantage as a maintenance therapy during 2 years of follow-up, with a 25% relapse rate, compared with 80% in the CM group (22). Because these studies did not include a maintenance medication condition, however, it remains unclear whether the m-CBT conferred additional benefit over standard maintenance pharmacotherapy.

An RCT examined the addition of mindfulness-based cognitive therapy (MBCT), compared with treatment as usual (TAU), in the prevention of relapse in patients with recurrent MDD currently in remission or recovery (25). Patients were required to have had at least 2 episodes in the last 5 years, with...
at least 1 of these within the last 2 years. MBCT is designed specifically for patients with former depression and is aimed at improving attentional competence so that earlier detection of, and intervention for, mood-linked negative thinking styles is enhanced. Patients in clinical remission from a depressive episode were randomized to receive TAU, or TAU plus MBCT, and followed for 1 year. Results indicated that, for patients who had experienced 3 or more previous depressive episodes, the rate of relapse for TAU was 66%, compared with 37% for TAU plus MBCT. This represented a medium effect size in favour of MBCT.

The authors thank the following for their contributions: Dr Raymund W Lam, Dr Gilbert D Pinard and Dr Ari E Zaretsky contributed to early drafts of this paper; Dr Jan Scott and Dr Michael Thase provided external peer review prior to publication.

**Table 5.2 Criteria for levels of evidence and lines of treatment recommendations**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Metaanalysis or replicated randomized controlled trial (RCT) that includes a placebo condition</td>
</tr>
<tr>
<td>2</td>
<td>At least 1 RCT with placebo or active comparison condition</td>
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<tr>
<td>3</td>
<td>Uncontrolled trial with 10 or more subjects</td>
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<tr>
<td>4</td>
<td>Anecdotal case reports</td>
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</table>

**Line of Treatment**

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>First-line</td>
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<tr>
<td>Second-line</td>
</tr>
<tr>
<td>Third-line</td>
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<tr>
<td>Not recommended</td>
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</tbody>
</table>

*Treatments with higher levels of evidence may be listed as lower lines of treatment due to clinical issues such as side effect or safety profile.*


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**REFERENCES**


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