Unipolar depression in adults: Treatment with antidepressant combinations

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INTRODUCTION

Antidepressant combinations are generally used for unipolar major depression (major depressive disorder) that is resistant to treatment with antidepressant monotherapy. Add-on pharmacotherapy is often necessary because initial treatment with a single antidepressant leads to remission in only 30 to 50 percent of patients [1-3]. Options for adjunctive pharmacotherapy include a second antidepressant, as well as second-generation antipsychotics, lithium, and triiodothyronine. Adjunctive psychotherapy is also an option.

Combining two antidepressants for treatment resistant depression is common [4]. As an example, retrospective studies of patients treated for depression with a single antidepressant (insurance claims database n >134,000; registry database n >240,000) found that a second antidepressant was added in approximately 10 percent of patients [5,6].

This topic reviews the indications and efficacy of combining antidepressants for patients with unipolar, nonpsychotic major depression. Choosing a drug regimen for major depression and using a second antidepressant as a hypnotic are discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression" and "Unipolar major depression in adults: Choosing initial treatment" and "Pharmacotherapy for insomnia in adults", section on 'Antidepressants'.)

INDICATIONS

Indications for antidepressant combinations include:

- Unipolar major depression that does not respond to multiple courses of treatment with antidepressant monotherapy as well as an antidepressant plus adjunctive pharmacotherapy (eg, antidepressant plus a second-generation antipsychotic, lithium, or triiodothyronine). (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Choosing a drug'.)

- Unipolar major depression characterized by prominent insomnia – An antidepressant (eg, SSRI or bupropion) can be augmented with another antidepressant such as low dose doxepin or trazodone. (See "Pharmacotherapy for insomnia in adults", section on 'Antidepressants'.)

We suggest that clinicians generally avoid combining antidepressants as initial treatment for unipolar major depression, because the evidence suggests that this approach does not provide any advantage over antidepressant monotherapy (see 'Initial treatment of depression' below). However, it is reasonable to initiate treatment with two antidepressants in patients who suffer a recurrent episode and who previously responded to antidepressant combinations after not responding to other antidepressant regimens.

PRESCRIBING ANTIDEPRESSANT COMBINATIONS

General principles — No evidence-based guidelines have been established for combining antidepressants in patients with unipolar major depression. Nevertheless, when clinicians combine antidepressants, we suggest using [7,8]:

- Drugs that do not pose greater safety or tolerability risks than monotherapy
- Drugs with distinct pharmacodynamic effects (mechanisms of action)
- Drugs with a limited range of pharmacodynamic effects
- Drugs that do not have opposing mechanisms of action
- Drugs with few or no pharmacokinetic interactions
- Drugs with simple metabolisms

In addition, the dose of antidepressants used in combination treatments should generally follow accepted dosing guidelines used in monotherapy for selected agents.

Drug-drug interactions — Certain antidepressant combinations should be avoided, such as a monoamine oxidase inhibitor (MAOI) plus a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor, which can cause the serotonin syndrome or a hypertensive crisis [7]. The combination of a tricyclic plus an MAOI is generally avoided as well due to the same safety concerns, and study results that show no benefit with this combination [9]. (See "Serotonin syndrome (serotonin toxicity)" and "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

Other antidepressant combinations that are reasonable may nevertheless cause problems that may be avoided by therapeutic drug monitoring. As an example, in a case series of three patients with unipolar major depression who did not respond to venlafaxine monotherapy, bupropion was added [10]. Bupropion increased venlafaxine levels, which in one patient led to agitation, headache, and insomnia; these adverse effects resolved with discontinuation of bupropion. Venlafaxine is a substrate of cytochrome P450 enzyme 2D6, whereas bupropion inhibits the enzyme.

Specific interactions between antidepressants may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Measurement based care — Outcomes for patients with major depression may be enhanced with measurement based care, which involves monitoring progress by serially measuring severity of symptoms with a standardized scale and using these measurements to adjust the treatment plan as necessary. Psychosocial functioning, side effects, and adherence can also be quantified. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

TREATMENT RESISTANT DEPRESSION

The term “treatment resistant depression” typically refers to major depressive episodes that do not respond satisfactorily after one or two trials of antidepressant monotherapy; however, the definition has not been standardized. Many patients with treatment resistant depression are prescribed a second antidepressant as add-on therapy. The sections below discuss the unclear benefit of this practice.

Additional information about treatment resistant depression in adults is discussed separately. (See "Unipolar treatment-resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

Unclear benefit from antidepressant combinations — Patients with unipolar, nonpsychotic major depression who do not respond to initial treatment with antidepressant monotherapy frequently receive add-on therapy with a second antidepressant from a different class (often referred to as combination therapy) [11]. Combination therapy with a second antidepressant is distinguished from add-on therapy with a medication that is not an antidepressant monotherapy, such as a second-generation antipsychotic or lithium.

While some randomized trials support combination therapy with two antidepressants, others do not. As an example, a systematic review identified five randomized trials in patients with treatment resistant depression (total n = 483) that compared an antidepressant plus a second antidepressant with an antidepressant plus placebo, and found that combination treatment was often not beneficial [12]. In three trials (total n = 387), response was comparable for patients who received either combination treatment or monotherapy, whereas the other two trials (total n = 96) found that response was superior with combination therapy. In the largest trial (n = 293), at least one adverse effect occurred in more patients who received the combination than in those who received monotherapy (77 versus 51 percent) [13].

Evidence that antidepressant combinations are not beneficial — For patients with treatment resistant depression, multiple placebo-controlled trials indicate that antidepressant combinations are not beneficial:

- A network meta-analysis of 48 randomized trials (n >6000 depressed patients) evaluated the efficacy of augmentation agents, including adjunctive bupropion, by using results from direct comparisons between the drugs, as well as indirectly comparing drugs through their relative effect with a common comparator (typically placebo) [14]. Remission with adjunctive bupropion and adjunctive placebo was comparable, as was response (reduction of baseline symptoms ≥50 percent).

- A subsequent, six-week randomized trial compared duloxetine plus bupropion with duloxetine plus placebo in 46 patients with treatment resistant depression, and found that response was comparable with adjunctive bupropion or placebo (26 and 22 percent of patients) [15].

- Another trial enrolled patients (n = 480) who had not responded to at least six weeks of antidepressant monotherapy and randomly assigned them to add-on treatment with mirtazapine (30 mg/day) or placebo for 12 weeks; patients receiving psychotherapy at baseline were allowed to continue it [16]. Remission was comparable with adjunctive mirtazapine and placebo (29 and 24 percent of patients); among patients receiving mirtazapine or placebo, adverse effects occurred in 50 and 30 percent.

Evidence that antidepressant combinations are beneficial — For patients who do not respond to initial antidepressant monotherapy, some randomized trials indicate that combining two antidepressants can be useful [17]. As an example:

- Two open-label 14-week randomized trials from the Sequenced Treatment Alternatives to Relieve Depression study compared the benefit of two antidepressants with an active control condition:
  - One trial compared bupropion sustained release (mean dose 268 mg per day) plus citalopram with buspirone (mean dose 41 mg per day) plus citalopram as next step treatment in 565 patients with major depression who did not respond to citalopram alone [18]. Reduction of symptoms was greater with bupropion plus citalopram; in addition, discontinuation of treatment due to side effects occurred in fewer patients with bupropion plus citalopram than buspirone plus citalopram (13 versus 21 percent).
  - The second trial compared mirtazapine (mean dose 36 mg per day) plus venlafaxine extended release (mean dose 210 mg per day) with tranylcypromine (mean dose 37 mg per day) alone in 109 patients who had not responded to three prior prospective courses of treatment [19]. Remission with tranylcypromine and with the combination was comparable (7 and 14 percent); however, symptom reduction was superior with mirtazapine plus venlafaxine. In addition, discontinuation of treatment due to side effects occurred in fewer patients who received the combination than tranylcypromine monotherapy (22 versus 41 percent). The average dose of tranylcypromine (37 mg per day) was such that few patients received a vigorous course of MAOI therapy.
- In addition, a four-week randomized trial compared bupropion sustained release with placebo as add-on treatment in 60 patients who had not responded adequately to four weeks of monotherapy with a selective serotonin reuptake inhibitor; only patients were blind to treatment [20]. Remission occurred in more patients who received adjunctive bupropion than placebo (60 versus 23 percent).

INITIAL TREATMENT OF DEPRESSION

Prescribing two antidepressants at the onset of treatment for unipolar nonpsychotic major depression does not appear to provide any advantage over antidepressant monotherapy. Although some randomized trials have found that antidepressant combinations are more efficacious than monotherapy, larger trials found no benefit in using antidepressant combinations.

Evidence that suggests antidepressant combinations are efficacious as initial treatment for unipolar major depression includes a meta-analysis of four randomized trials (250 patients) that initiated treatment with an antidepressant combination or antidepressant monotherapy [21]. Remission was nearly three times more likely with combination treatment (relative risk 2.7, 95% CI 1.7-4.4), and discontinuation of treatment due to adverse effects was comparable for the two groups. Medication combinations included:

- Mirtazapine plus selective serotonin reuptake inhibitors (fluoxetine or paroxetine)
- Mirtazapine plus bupropion
- Mirtazapine plus venlafaxine
- Selective serotonin reuptake inhibitors (citalopram or fluoxetine) plus tricyclics (desipramine or nortriptyline)

However, larger randomized trials (conducted after the meta-analysis) found that for initial treatment of unipolar major depression, antidepressant combinations and antidepressant monotherapy were comparable:

- A 12-week trial compared escitalopram plus placebo, escitalopram plus sustained release bupropion, and mirtazapine plus extended release venlafaxine in 665 patients with unipolar major depression; only patients were blind to treatment allocation [22]. Remission occurred in approximately 39 percent of the patients in each group, and tolerability was poorer with mirtazapine plus venlafaxine than escitalopram plus placebo.

- Another 12-week trial compared escitalopram plus bupropion extended release, escitalopram alone, and bupropion alone in 245 patients with unipolar major depression; remission was comparable for the three groups [23].

Melancholic features were present in most patients who participated in trials that found antidepressant combinations were superior to antidepressant monotherapy [24,25]. By contrast, melancholic features were present in only a minority of patients in trials that did not find any benefit in using antidepressant combinations [22,23]. The presence of melancholic features may indicate a greater severity of illness that is more amenable to aggressive treatment at the outset [26,27].

In addition, different antidepressant medication combinations may differ in efficacy. The meta-analysis described above in this section focused largely on combinations with mirtazapine [21], while the two large randomized controlled trials both evaluated selective serotonin reuptake inhibitor plus bupropion [22,23].

Additional information about the initial treatment of unipolar major depression is discussed separately. (See "Unipolar depression in adults and initial treatment: General principles and prognosis" and "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments" and "Unipolar depression in adults: Investigational and nonstandard treatment".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- Indications for combining two antidepressants include unipolar major depression that does not respond to multiple courses of treatment with antidepressant monotherapy as well as an antidepressant plus adjunctive pharmacotherapy (eg, antidepressant plus a second-generation antipsychotic or lithium). (See 'Indications' above and "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Choosing a drug'.)

- When prescribing antidepressant combinations, it is preferable to use antidepressants with distinct mechanisms of action. Certain antidepressant combinations should be avoided, such as a monoamine oxidase inhibitor plus a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor. (See 'Prescribing antidepressant combinations' above.)

- Patients with unipolar, nonpsychotic major depression who do not respond to initial treatment with antidepressant monotherapy often receive add-on therapy with a second antidepressant; however, it is not clear that this practice is beneficial, due to inconsistent results from randomized trials. (See 'Treatment resistant depression' above.)

- Prescribing two antidepressants at the onset of treatment for unipolar nonpsychotic major depression does not appear to provide any advantage over antidepressant monotherapy. (See 'Initial treatment of depression' above.)

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