



# Is combination pharmacotherapy effective for patients with acute depression?

A systematic review and meta-analysis found that these combinations were superior to monotherapy and had comparable tolerability.

## PRACTICE CHANGER

Use a combination of a presynaptic  $\alpha$ 2-autoreceptor antagonist (eg, mirtazapine or trazodone) and a monoamine reuptake inhibitor (eg, selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], or tricyclic antidepressant [TCA]) to treat acute depression in adult patients.

### STRENGTH OF RECOMMENDATION

**A:** Based on a single systematic review with meta-analysis.<sup>1</sup>

Henssler J, Alexander D, Schwarzer G, et al. Combining antidepressants vs antidepressant monotherapy for treatment of patients with acute depression: a systematic review and meta-analysis. *JAMA Psychiatry*. 2022;79:300-312. doi: 10.1001/jamapsychiatry.2021.4313

## ILLUSTRATIVE CASE

A healthy 33-year-old woman presents to your office with a 3-month history of depressed mood. She reports difficulty concentrating, insomnia, decreased appetite, and generalized fatigue. She denies suicidal or homicidal ideation, substance misuse, or history consistent with manic episodes. Her vital signs are normal and overall her physical examination is unremarkable, although the patient is tearful when discussing her mood. Using shared decision-making, you and the patient determine it is appropriate to initiate pharmacotherapy. Is there a role for combination pharmacotherapy to treat this patient's acute depression?

Unipolar depression is a highly prevalent condition, estimated to affect 21% of US adults at some point in their lifetime.<sup>2</sup> It is the second leading cause of disability in the United States, with an estimated economic impact of more than \$200 billion annually.<sup>3</sup>

The diagnosis of unipolar depression is based on the criteria set forth in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* and commonly includes depressed mood, anhedonia, sleep disturbance, appetite changes, fatigue, feelings of worthlessness or guilt, decreased ability to concentrate, and psychomotor symptoms occurring over at least a 2-week period.<sup>4</sup> Symptoms represent a decrease in functioning from previous levels that are not attributable to another medical condition or substance, and must not include a history of past manic or hypomanic episodes. Thoughts of death and suicidal ideation are common.

Several systematic reviews and meta-analyses have shown that a combination of psychotherapy and pharmacotherapy is more efficacious for treatment of unipolar depression than either therapy alone.<sup>5-7</sup> As for which medication is most effective and tolerable, multiple systematic reviews and meta-analyses have not demonstrated superiority of 1 second-generation antidepressant (eg, SSRIs, SNRIs) over another.<sup>7,8</sup>

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**Brock Cardon, MD, FAAFP; Stephanie Schirding, MD**  
Nellis Air Force Base Family Medicine Residency, NV

**DEPUTY EDITOR**  
**Gary Asher, MD, MPH**  
Department of Family Medicine, School of Medicine, University of North Carolina at Chapel Hill

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➤ **This study suggests that combination pharmacotherapy is superior to monotherapy, both at the time of treatment initiation and in patients with previous inadequate pharmacologic response.**

General practice guidelines support titration of the dose or a switch in monotherapy medications until treatment response is achieved, prior to initiation of a second agent. When an adjunctive medication is considered, there are several options: a second-generation antipsychotic, a second antidepressant from a different class, thyroid hormone, and lithium. Special consideration is given to the adverse effect profile and potential tolerability; higher adverse effect profiles are observed with second-generation antipsychotics and lithium.<sup>9</sup>

It is not common practice to initiate 2 antidepressants for a new diagnosis of acute depression. The systematic review and meta-analysis conducted by Henssler et al<sup>1</sup> attempted to provide evidence to support the efficacy and tolerability of specific antidepressants when used in combination for initial treatment of acute depression. Of note, a 2008 national survey showed that a majority of psychotropic medications in the United States are prescribed by primary care physicians (73.6%) rather than psychiatrists, making this analysis relevant to family physicians.<sup>10</sup>

#### STUDY SUMMARY

##### **Combination pharmacotherapy yields superior efficacy in acute depression**

This 2022 systematic review and meta-analysis (39 randomized clinical trials [RCTs]; N = 6751) compared the efficacy and tolerability of monotherapy to combination therapy in the treatment of patients with acute depression.<sup>1</sup> The study also aimed to address which specific combination therapies were superior.

Selected RCTs included an intervention group using a combination of 2 antidepressants, regardless of dosage, and a control group of patients taking antidepressant monotherapy. Studies evaluated both patients being treated for the first time and those with a previously inadequate response to medical treatment. All participants were ages 18 years or older (mean age not reported) and had received a diagnosis of depressive disorder according to standard operationalized criteria; patients with multiple psychiatric comorbidities were not excluded.

Studies used various standardized questionnaires—most frequently, the Hamilton Depression Rating Scale (HDRS) and the

Montgomery-Åsberg Depression Rating Scale (MADRS)—to determine the severity of depression at baseline and following treatment. The HDRS is a 17-item depression scale and the MADRS is a 10-item depression scale; for both, higher scores indicate worsening depression. Follow-up time ranged from 2 to 12 weeks.

The primary outcome was treatment efficacy measured as the standardized mean difference (SMD). Secondary outcomes included remission (normal-range scores) and response to treatment (eg,  $\geq 50\%$  reduction in scores), as defined by the study authors.

Combination therapy was determined to have superior efficacy relative to monotherapy (SMD = 0.31; 95% CI, 0.19-0.44;  $P < .001$ ). Combinations with a presynaptic  $\alpha 2$ -autoreceptor antagonist (eg, mirtazapine, trazodone, or mianserin [the last of which is not approved by the US Food and Drug Administration for use in the United States]) and a monoamine reuptake inhibitor (eg, an SSRI, SNRI, or TCA) were superior to other combinations (SMD = 0.37; 95% CI, 0.19-0.55). Combinations that included bupropion were not superior to monotherapy (SMD = 0.10; 95% CI, -0.07 to 0.27).

Secondary outcomes revealed combination therapy to be superior to monotherapy with respect to remission (odds ratio [OR] = 1.52; 95% CI, 1.20-1.92) and response (OR = 1.40; 95% CI, 1.15-1.69). Subgroup analyses showed that combinations with presynaptic  $\alpha 2$ -autoreceptor antagonists led to improved remission (OR = 1.42; 95% CI, 1.01-2.01) and response (OR = 1.49; 95% CI, 1.18-1.87) compared with monotherapy, whereas combinations that included bupropion were not superior to monotherapy. For patients who dropped out of treatment for any reason, including adverse drug events, results for combination pharmacotherapy and monotherapy were similar.

#### WHAT'S NEW

##### **One combination proved more effective than others**

Current clinical guidelines indicate the suitability of trialing pharmacologic monotherapy during the acute phase of depression treatment prior to initiating an adjunctive medication.<sup>9</sup> All classes of medication investigated in this meta-analysis are generally regarded as first-

line therapies, although they are rarely started in combination. This study's findings suggest that combination pharmacotherapy, especially with a presynaptic  $\alpha$ 2-autoreceptor antagonist (eg, mirtazapine, trazodone) and a monoamine reuptake inhibitor (eg, an SSRI, SNRI, or a TCA), is superior to monotherapy, both at the time of treatment initiation and in patients with previous inadequate pharmacologic response.

### CAVEATS

#### Potential limitations due to publication bias

Concerns about publication bias and significant study heterogeneity may limit the generalizability of these findings. However, conclusions were robust in a subgroup analysis that was restricted to publications with low risk for bias.

### CHALLENGES TO IMPLEMENTATION

#### None to report

There are no major challenges to implementing this combination treatment. Importantly, there were no differences in tolerability between monotherapy and combination treatment. **JFP**

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## Dx ACROSS THE SKIN COLOR SPECTRUM

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patients and work closely on long-term management. The treatment options for melasma are considered cosmetic and may be cost prohibitive for many to cover out of pocket. Topical treatments have been found to be the most cost-effective.<sup>13</sup> Some compounding pharmacies and drug discount programs provide more affordable treatment pricing; however, some patients are still unable to afford these options. **JFP**

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