POEMs

Patient-Oriented Evidence That Matters

Combination Antidepressant Therapy Is More Effective Than Monotherapy for Acute Severe Depression and Nonresponding Depression

Clinical Question

What are the efficacy and tolerability of combination therapy compared with monotherapy for acute severe depression and recurrent depression in adults?

Bottom Line

The review found that combination therapy using a reuptake inhibitor (i.e., a selective serotonin reuptake inhibitor, serotonin-noradrenaline reuptake inhibitor, or tricyclic antidepressant) with an alpha$_2$-adrenergic receptor antagonist (mirtazapine [Remeron] or trazodone) is more effective than monotherapy for first-line treatment of acute severe depression and for patients who do not respond to monotherapy. Dropout rates due to adverse events are similar for combination therapy and monotherapy. (Level of Evidence = 1a)

Synopsis

The optimal management of an initial episode of acute severe depression and nonresponsive depression in adults remains uncertain. The investigators thoroughly searched, without language restrictions, multiple databases, including MEDLINE, PsycINFO, Embase, and the Cochrane Central Register of Controlled Trials, for randomized trials that compared antidepressant monotherapy with a combination of two antidepressants. Eligible trials included first-line antidepressant treatment and patients with depression resistant to initial therapy. In studies that included depression that did not respond to monotherapy (control group), patients received continued monotherapy with the same antidepressant at the same or higher dose or monotherapy with a different antidepressant. Two individuals independently evaluated trials for study eligibility and risk of bias using the Cochrane scoring tool. Disagreements were resolved by consensus agreement. The primary outcome was treatment efficacy measured as the standardized mean difference. Of the 39 trials, 15 were classified as low risk of bias. Heterogeneity was minimal when restricted to studies with low risk of bias, and an analysis for publication bias found minimal risk for altering the results.

Combination therapy provided superior efficacy vs. monotherapy for first-line treatment and for depression that did not respond to monotherapy (standardized mean difference = 0.31; 95% CI, 0.19 to 0.44). Results were similar when restricting the analyses to only studies with low risk of bias. The combination of a monoamine reuptake inhibitor with an alpha$_2$-adrenergic receptor antagonist is associated with superior efficacy compared with monotherapy for first-line treatment and for depression that did not respond to monotherapy. Combination therapy with bupropion (Wellbutrin) was not associated with superior outcomes compared with monotherapy for first-line treatment, but it was superior for depression that did not respond to monotherapy. Drop-out rates due to adverse events were similar for both types of therapy.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Industry and foundation

Setting: Various (meta-analysis)

Reference: *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(4):300-312.*

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SGLT-2 Inhibitors Reduce Heart Failure–Related Hospitalization in Patients Without Diabetes

Clinical Question

Is treatment with sodium-glucose cotransporter-2 (SGLT-2) inhibitors effective in decreasing hospitalization for patients with heart failure, with or without diabetes mellitus?

Bottom Line

In patients with heart failure without diabetes, adding an SGLT-2 inhibitor to treatment will have a modest effect on

decreasing the likelihood of hospitalization for heart failure. In a previous meta-analysis with fewer studies overall, mortality risk was not reduced, although cardiovascular mortality was slightly decreased. Several guideline development groups have added SGLT-2 inhibitors to their treatment algorithms. (Level of Evidence = 1a)

Synopsis

The researchers followed PRISMA guidelines for conducting and reporting the analysis. They searched four databases, including the Cochrane Library, as well as reference lists and other systematic reviews, and they polled experts. They identified eight randomized controlled trials, published in English, enrolling a total of 15,022 patients with heart failure who were followed up for at least six months. Most of the trials were at low risk of bias, and heterogeneity among study results was very low. Adding SGLT-2 inhibitor treatment to existing therapy reduces the risk of hospitalization over the first six months by approximately one-third (i.e., 41 to 78 fewer hospitalizations per 1,000 people treated). All-cause mortality was not affected by treatment, but cardiovascular mortality was decreased with treatment (i.e., 2 to 41 fewer deaths per 1,000 patients treated over one year). There was no difference in outcomes for patients with or without diabetes or preserved or reduced ejection fraction. The effect of treatment was greater in the first year and in patients with a poorer prognosis. The analysis did not attempt to differentiate effectiveness among the SGLT-2 inhibitor options.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Foundation

Setting: Various (meta-analysis)

Reference: *Zou X, Shi Q, Vandvik PO, et al. Sodium-glucose cotransporter-2 inhibitors in patients with heart failure: a systematic review and meta-analysis.* Ann Intern Med. *2022;175(6):851-861.*

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Aducanumab Is Not Effective for Mild Cognitive Impairment or Mild Alzheimer Dementia and Has Major Safety Issues

Clinical Question

Is aducanumab (Aduhelm) safe and effective for the treatment of mild cognitive impairment or mild Alzheimer disease?

Bottom Line

This drug was approved by the U.S. Food and Drug Administration (FDA) after its advisory panel voted 10 to 1 against approval, with three members resigning in protest after the FDA decision became public. The drug costs $56,000 per year, which does not include the cost of regular magnetic resonance imaging, physician fees, and the management of complications. This drug has no meaningful impact on symptoms. (Level of Evidence = 1b–)

Synopsis

A report was published on two trials that compared aducanumab with placebo for mild cognitive impairment or mild Alzheimer disease. The studies were the basis for the FDA's approval of the drug over the strong objections of its advisory panel. The EMERGE (n = 1,643) and ENGAGE (n = 1,653) trials identified adults with mild Alzheimer disease or mild cognitive impairment, and evidence of amyloid deposition on positron emission tomography scan. The trials included patients with a Mini-Mental State Examination (MMSE) score between 24 and 30 (30 = normal) and a Clinical Dementia Rating Scale score of 0.5. Patients with evidence of intracranial pathology, including microhemorrhages, hemorrhages, and infarcts, were excluded. Approximately one-fourth of screened patients met these criteria. Patients in each study were randomized to receive placebo, low-dose aducanumab, or high-dose aducanumab, with the dose differing according to the presence or absence of apolipoprotein E4. The trials were halted early for futility, with slightly more than one-half of patients completing the full 75-week follow-up. The authors argue that the trials should not have been stopped, and they presented the data for those patients who completed the full study period. In the report, the results are given for all patients receiving at least one dose of the study drug. The authors found that aducanumab successfully reduced amyloid deposition. Although there were small and sometimes statistically significant changes in the MMSE, Clinical Dementia Rating Scale, and Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-COG) scores, none came close to exceeding the minimum clinically important difference. This is the minimum the score would have to improve before a patient or caregiver is likely to notice improvement.

A separate pooled analysis (https://www.aafp.org/afp/2022/0400/p353.html) showed no statistically or clinically significant improvement in the MMSE and Clinical Dementia Rating Scale scores, and the improvement in the ADAS-COG score was far lower than the minimum clinically important difference of 3 points. With regard to harms, approximately one-fourth of the patients in the low-dose group and more than one-third in the high-dose group developed amyloid-related imaging abnormalities with brain effusion or edema, whereas 16% in the low-dose group and 20% in the high-dose group developed brain microhemorrhages; these changes mandated temporary

discontinuation of the drug. Serious or severe adverse events occurred in 16 patients and included gait disturbance, confusion, and seizures.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Uncertain

Setting: Outpatient (specialty)

Reference: *Haeberlein SB, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease.* J Prev Alzheimers Dis. *2022;9(2):197-210.*

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Less Than 4% of Children With Newly Diagnosed Hypertension in Primary Care or School Settings Have Secondary Causes

Clinical Question

How often do children with newly diagnosed hypertension have secondary hypertension?

Bottom Line

In school or primary care settings, less than 4% of children with newly diagnosed hypertension have secondary causes compared with 20% of those referred to specialty clinics. These data are reassuring that children in primary care settings do not need extensive workup or specialty referrals. (Level of Evidence = 2a)

Synopsis

The authors searched several databases to identify studies that reported the prevalence of secondary hypertension among children with newly diagnosed hypertension. The authors included 26 studies of 2,575 children with hypertension: 19 studies were prospective and seven were retrospective; 18 studies were in school or primary care settings; and in eight studies, the participants were referred to nephrology or hypertension clinics. The studies were at low or moderate risk of bias. Although the approaches to diagnosing secondary hypertension varied, all were acceptable based on current guidelines. Among the participants, 457 (17.7%) were found to have secondary hypertension, but with a high degree of heterogeneity. The prevalence of secondary hypertension was markedly different by setting (3.7% in school or primary care settings; 20.1% in referral settings), but significant heterogeneity remained (78.9% and 94.6%, respectively). The authors found no evidence of publication bias.

Study design: Meta-analysis (other)

Funding source: Unknown/not stated

Setting: Various (meta-analysis)

Reference: *Nugent JT, Young C, Funaro MC, et al. Prevalence of secondary hypertension in otherwise healthy youths with a new diagnosis of hypertension: a meta-analysis.* J Pediatr. *2022;244:30-37.e10.*

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