Cochrane for Clinicians

Putting Evidence into Practice

Antidepressants Plus Benzodiazepines for Adults with Major Depression

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Clinical Question

Is treatment with antidepressants plus benzodiazepines more effective than antidepressants alone for adults with major depression?

Evidence-Based Answer

A combination of tricyclic antidepressants and benzodiazepines is more effective for major depression in adults than tricyclic antidepressants alone in the first four weeks of treatment (standardized mean difference [SMD] = −0.25; 95% CI, −0.46 to −0.03). This effect is not sustained beyond four weeks of therapy. Use of benzodiazepines must be balanced against the risk of adverse effects, including dependence, tolerance, accident proneness, teratogenicity, and increased costs.[1] (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

In the United States, 17.3 million adults had at least one major depressive episode in 2017.[2] Although initiating benzodiazepine therapy with antidepressants is a common choice for managing major depression globally, most treatment guidelines recommend antidepressant monotherapy as a first-line approach. The authors of this Cochrane review updated previously published reviews from 2001 and 2005 that assessed the effects of a combination of antidepressants and benzodiazepines vs. antidepressants alone to treat major depression in adults.

This updated Cochrane review included nine randomized controlled trials published between 1978 and 2002 and one reanalysis of a 1998 study that was published in 2010.[1] The review involved 731 ambulatory patients and inpatients 18 years and older with depression (diagnosed using the second, third, or fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* depending on the year of the study) in the United States (six studies), Netherlands, Spain, Norway, and Japan. Trials were excluded for not being randomized, relying on self-reported patient data alone, lacking outcomes, or having a high risk of bias. Seven studies used tricyclic antidepressants, two used fluoxetine (Prozac), and one used another antidepressant class. A variety of short- and long-acting benzodiazepines were assessed. There was general agreement between study outcomes with no outliers noted.

The studies examined the effect of a combination of antidepressants and benzodiazepines vs. antidepressants alone during three depression treatment phases: early (four weeks or less), acute (five to 12 weeks), and continuous (more than 12 weeks) using the difference in depression severity scores (current score minus baseline score). They used the Hamilton Rating Scale for Depression, a clinician-administered 21-item depression screening questionnaire that evaluates typical depression symptoms (e.g., mood, guilt, agitation, insomnia) at the initiation of therapy and throughout treatment to assess effectiveness and remission of symptoms.

Combination therapy demonstrated a small but significant reduction in symptoms compared with monotherapy in the early phase (SMD = −0.25; 95% CI, −0.46 to −0.03; 10 studies; N = 598; moderate-quality evidence downgraded because of risk of bias). There was likely no difference between treatments in the acute phase (SMD = −0.18; 95% CI, −0.40 to 0.03; seven studies; n = 347; low-quality evidence downgraded because of risk of bias and low number of participants) or the continuous phase (SMD = −0.21; 95% CI, −0.76 to 0.35; one study; n = 50; low-quality evidence downgraded because of risk of bias and low number of participants).

These are summaries of reviews from the Cochrane Library.

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CME **This clinical content** conforms to AAFP criteria for CME. See CME Quiz on page 519.

There was no difference in treatment dropout rate for any reason between combined therapy and antidepressants alone. Although specific adverse effects were not reported, benzodiazepine use was associated with potential somnolence and a presumed increased risk of accidents, and in this review patients treated with combined therapy reported experiencing at least one adverse effect more often than those who received antidepressants alone (number needed to harm = 18; 95% CI, 13 to 83; relative risk = 1.12; 95% CI, 1.01 to 1.23; seven studies; n = 510; moderate-quality evidence). This finding was consistent across included studies.

The U.S. Preventive Services Task Force and American Academy of Family Physicians recommend screening for depression in the general adult population. Screening must be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up.[3] Current depression treatment guidelines do not recommend using benzodiazepines for major depression and favor antidepressant monotherapy as the first-line pharmacologic approach.[4,5] Most guidelines recommend using selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, mirtazapine (Remeron), and bupropion (Wellbutrin) as first-line agents. The antidepressants used most often in these studies would be considered second-line treatments. There were not enough data to directly compare selective serotonin reuptake inhibitors and tricyclic antidepressants with and without benzodiazepines in this systematic review. Although this review suggests that patients may benefit from combination therapy, there are multiple unanswered questions, including which patients benefit most from combination therapy, how to predict who may be at increased risk of addiction or tolerance, and how to best discontinue benzodiazepine use after four weeks.

The practice recommendations in this activity are available at http://www.cochrane.org/CD001026.

Editor's Note: The number needed to harm reported in this Cochrane for Clinicians was calculated by the author based on raw data provided in the original Cochrane review.

References

1. Ogawa Y, Takeshima N, Hayasaka Y, et al. Antidepressants plus benzodiazepines for adults with major depression. *Cochrane Database Syst Rev.* 2019;(6):CD001026.
2. Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health (NSDUH) 2018 annual report. Accessed October 12, 2019. https://www.samhsa.gov/data/
3. U.S. Preventive Services Task Force. Final recommendation statement: depression in adults: screening. May 2019. Accessed October 12, 2019. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/depression-in-adults-screening1
4. American Psychiatric Association. *American Psychiatric Association Practice Guideline for the Treatment of Major Depressive Disorder.* American Psychiatric Publishing; 2010.
5. National Institute for Health and Care Excellence. Depression in adults with a chronic physical health problem: recognition and management. Clinical guideline [CG91]. October 2009. Accessed March 26, 2020. http://www.nice.org.uk/guidance/CG91

Lithium for Acute Mania

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Clinical Question

Is lithium a safe and effective therapy for episodes of acute mania?

Evidence-Based Answer

Lithium is more effective at inducing a reduction of at least 50% on the validated Young Mania Rating Scale (YMRS) compared with placebo (number needed to treat [NNT] = 6; 95% CI, 5 to 8; six studies; n = 1,707). (Strength of Recommendation [SOR]: A, based on consistent, good-quality patient-oriented evidence.) Most comparisons of lithium with mood stabilizers and antipsychotics demonstrate little to no difference in effectiveness; however, olanzapine (Zyprexa) is slightly more effective than lithium. When compared with placebo, lithium increases the risk of tremor (number needed to harm [NNH] = 11; 95% CI, 7 to 21; six studies; n = 1,241) and somnolence (NNH = 19; 95% CI, 10 to 50; seven studies; n = 1,351).[1] (SOR: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Bipolar disorder is a common disease in which patients experience some combination of depressed mood, elevated mood (mania), and mixed states. Lithium is effective as a maintenance

drug in bipolar disorder, acting as a mood stabilizer and decreasing the risk of suicide.

This Cochrane review evaluated lithium as a first-line therapy for acute mania, and included 36 randomized controlled trials and 4,220 patients.[1] Three of the studies included patients younger than 18 years. The other studies included male and female patients of any age with bipolar disorder who fit criteria for a manic episode. The studies compared lithium with placebo, electroconvulsive therapy, and 12 other medications over three to 12 weeks. The study authors used odds ratios to analyze binary efficacy outcomes.

A positive response was substantiated by a reduction of at least 50% in symptoms on the YMRS. Patients who had acute mania treated with lithium vs. placebo were more likely to achieve this effect (NNT = 6; 95% CI, 5 to 8; six studies; n = 1,707). Lithium also allowed patients to achieve remission of acute mania earlier than placebo (NNT = 6; 95% CI, 5 to 8; five studies; n = 1,597). These trials predominantly occurred over three to four weeks, with the longest comparison lasting eight weeks.

For direct drug comparisons, lithium appeared less likely to induce a reduction of at least 50% in symptoms on the YMRS vs. olanzapine (NNT = 6; 95% CI, 3 to 84; two studies; n = 180; low-certainty evidence downgraded from moderate because of the risk of publication bias and low number of studies). Lithium was more effective than topiramate (Topamax) at treating acute mania (NNT = 6; 95% CI, 4 to 10; one study; n = 660; high-certainty evidence; 12-week trial). There was no evidence that lithium was better or worse at treating mania than any of the other studied medications, nor was there enough evidence to draw a conclusion about electroconvulsive therapy.

Compared with placebo, lithium was more likely to cause tremor (NNH = 11; 95% CI, 7 to 21; six studies; n = 1,241; high-certainty evidence) and somnolence (NNH = 19; 95% CI, 10 to 50; seven studies; n = 1,351; high-certainty evidence). Additional reported adverse effects of lithium therapy included nausea, vomiting, polyuria, polydipsia, and anorexia.[2] The adverse effect profile of olanzapine is similar, with the addition of extrapyramidal symptoms.

The National Institute for Health and Care Excellence guidelines note that in a secondary care setting, patients with acute mania should be treated with antipsychotics. However, if a maximum dose of an antipsychotic is ineffective, lithium should be considered.[3] This Cochrane review suggests that physicians use lithium to treat acute mania because it is similarly effective to other agents and more effective than placebo. Consideration should be given to the potential adverse effects and monitoring required for lithium, as well as any other agent, before administering treatment, keeping in mind the risks and benefits to the individual patient.

The practice recommendations in this activity are available at http://www.cochrane.org/CD004048.

Editor's Note: The NNTs, NNHs, and CIs reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review.

References

1. McKnight RF, de La Motte de Broöns de Vauvert SJGN, Chesney E, et al. Lithium for acute mania. *Cochrane Database Syst Rev.* 2019;(6):CD004048.
2. Dols A, Sienaert P, van Gerven H, et al. The prevalence and management of side effects of lithium and anticonvulsants as mood stabilizers in bipolar disorder from a clinical perspective: a review. *Int Clin Psychopharmacol.* 2013; 28(6):287-296.
3. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. Updated February 2020. Accessed April 6, 2020. https://www.nice.org.uk/guidance/cg185/chapter/1-Recommendations#managing-mania-or-hypomania-in-adults-in-secondary-care-2 ■