# Review: Low dose was as effective as standard dose tricyclic antidepressants in adults with depression

Furukawa TA, McGuire H, Barbui C. **Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review.** BMJ. 2002;325:991-5.

## QUESTION

In patients having acute-phase treatment for depression, what is the comparative effectiveness and safety of low-dose (LD) and standard-dose (SD) tricyclic antidepressants or placebo?

## DATA SOURCES

Studies were identified by searching the Cochrane Collaboration Depression, Anxiety, and Neurosis Controlled Trials Register (up to November 2000) and SciSearch; hand searching bibliographies of relevant studies; and consulting authors and experts.

## STUDY SELECTION

Randomized trials lasting ≥ 4 weeks that compared LD tricyclics with placebo or SD in adults for the acute phase of treatment for depression. LD was defined as ≤ 100 mg/d of imipramine or equivalent; SD was defined as > 100 mg/d.

## DATA EXTRACTION

2 reviewers independently assessed study methods, quality, and outcomes. Treatment response was defined as ≥ 50% reduction in the severity of depression.

## MAIN RESULTS

35 studies (2013 patients) compared LD tricyclics with placebo, and 6 studies (551 patients) compared LD with SD tricyclics. 16 studies used amitriptyline and 13 used imipramine. 10 studies were done in primary care and 12 in psychiatric settings. Mean dosages of LD tricyclics were mostly between 75 and 100 mg/d. LD improved treatment response more than did placebo at 4 weeks and at 6 to 8 weeks (Table). LD and SD tricyclics did not differ for treatment response at 4 or 6 to 8 weeks (Table). SD tricyclics led to more dropouts caused by side effects than LD tricyclics, and LD tricyclics led to more dropouts caused by side effects than placebo.

## CONCLUSION

In adults, low-dose (75 to 100 mg/d) tricyclic antidepressants are more effective than placebo and as effective as standard-dose (> 100 mg/d) tricyclic antidepressants and are associated with fewer dropouts from side effects than standard-dose regimens.

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**Low-dose (LD) vs placebo (P) or standard-dose (SD) tricyclic antidepressants for treatment response (≥ 50% reduction in severity) in depression**

| Follow-up (number of studies) | Comparison | Weighted event rates | RBI (95% CI) | NNT (CI) |
|---|---|---|---|---|
| 4 wk (23) | LD vs P | 55% vs 29% | 65% (36 to 99) | 4 (3 to 6) |
| 6 to 8 wk (14) | LD vs P | 64% vs 38% | 44% (12 to 84) | 4 (3 to 8) |
| | | | RBR (CI) | NNH |
| 4 wk (7) | LD vs SD | 41% vs 53% | 11% (–7 to 25) | Not significant |
| | | | RBI (CI) | NNT |
| 6 to 8 wk (4) | LD vs SD | 42% vs 39% | 13% (–17 to 53) | Not significant |

*RBR = relative benefit reduction. Other abbreviations defined in Glossary; RBI, RBR, NNT, NNH, and CI calculated from data in article using a random-effects model.

## COMMENTARY

Primary care physicians are frequently criticized for undertreatment of depression, including underdosing of tricyclic antidepressants. This careful review by Furukawa and colleagues suggests that this criticism may not be fully justified. The methodological quality of the included studies was adequate, and the sample size was sufficient to support clear conclusions.

Furukawa and colleagues find that the evidence is consistent in 2 related aspects: low-dose tricyclic regimens are superior to placebo, and low-dose regimens are similar in effect to higher-dose treatment. The studies addressing the first question, however, overlap only minimally with those addressing the second. This leaves open the possibility that low-dose and standard-dose tricyclic treatments were equally *in*effective in the trials directly comparing them, rather than equally effective. This remaining uncertainty, among other reasons, helps us understand why the Depression and Bipolar Support Alliance (an advocacy group for persons with mood disorders) recently affirmed the value of placebo control groups in depression treatment trials. In the absence of sufficient placebo-controlled trials comparing low-dose with standard-dose tricyclic treatment, we should probably regard these meta-analytic results as strongly suggestive rather than definitive. However, based on this evidence, clinicians could consider using low-dose regimens as an acceptable plan for patients with depression in whom tricyclics are to be used.

We should also recall that a finding of equal efficacy generally does not imply equal efficacy for every patient. If tricyclic treatment at low doses does not produce a clinical response, increasing the dose above 100 mg/d should be considered.

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