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Review: Low dose tricyclic antidepressants may be effective for adults with acute depressive disorder

Furukawa T, McGuire H, Barbui C. *Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review*. *BMJ* 2002 Nov;325:991-1000.

QUESTION: What are the beneficial and adverse effects of low dose tricyclic antidepressants for adults with acute phase depression?

Design

Systematic review with meta-analysis.

Data sources

Studies were identified using the Cochrane Collaboration depression, anxiety and neurosis controlled trials register (to November 2000) which incorporates

searches of Medline, Embase, CINAHL, PsycInfo, PSYNDEx and LILACS. Major psychiatric and medical journals and bibliographies were hand searched and experts were contacted for additional studies.

Study selection

Eligible studies were randomised trials lasting at least 4 weeks that compared low dose tricyclics with placebo or standard dose tricyclics in adults with acute phase depression. "Low dose" was defined as less than or equal to 100 mg per day, most commonly between 75 and 100 mg/day. Nortriptyline was excluded because the standard dose is debatable. 35 studies with 2013 participants compared low dose tricyclics with placebo. 6 studies with 551 participants compared low dose tricyclics with standard dose tricyclics.

Data extraction

Data were extracted on sample size, study design, participant characteristics, interventions and outcomes. The main outcome measures were response to treatment, overall dropouts and dropouts due to adverse effects (relative risk using a random effects model). Response was defined according to classifications in the original papers, but usually involved a 50% or greater reduction in severity of depression.

Main results

People receiving low dose tricyclics were 1.65 times more likely to respond to treatment at 4 weeks compared to placebo (95% CI 1.6 to 2.0) and 1.47 times more likely to respond to treatment at 6-8 weeks (95% CI 1.12 to 1.94). People receiving standard dose tricyclics were not clearly more likely to respond to treatment than those receiving low dose tricyclics (relative risk at 4 weeks 0.89, 95% CI 0.74 to 1.07; relative risk at 6-8 weeks 1.11, 95% CI 0.76 to 1.61). Standard dose tricyclics had a higher dropout rate due to adverse effects compared to low dose tricyclics.

Conclusions

Low dose tricyclics may be effective for some adults with depressive disorder. It is uncertain if standard dose therapy is more effective, but low dose therapy results in fewer dropouts due to adverse effects. Minimum effective dose ranges have yet to be established.

Source of funding:
St Luke's Life Science
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COMMENTARY

This controversial review raised many reactions (www.bmj.com). It addresses the *minimally effective* dose of tricyclic antidepressants (TCAs) for depression. It does not examine the *optimal* dose (best efficacy with good tolerability). Nor does it address *when* higher doses should be used: immediately (at the onset of treatment) or for non-responders to the minimal effective dose after several weeks?

The review suggests that a TCA prescribed at doses below 100 mg might be beneficial, especially in psychiatric settings. The results do not rule out superior efficacy of standard doses, however. There are several methodological weaknesses: (1) The studies were highly heterogeneous; (2) Study characteristics are described poorly which impairs external validity; (3) Transparency is limited because only relative risks are presented, often without pooled control event rates; (4) Only four studies (116 participants) include long term comparisons (3-12 months), so conclusions about longer treatment are questionable; (5) More importantly, the effect sizes of the major analyses decrease considerably when a rigorous intention to treat analysis is applied. For instance, the overall number needed to treat for 6-8 week trials increases from 6 (95% CI 3 to 22) to 10 (95% CI 3 to ∞); (6) Relative risks are also lower in primary care settings (1.23 for 6-8 week trials, 95% CI 0.97 to 1.55), where lower doses of TCAs are most frequently prescribed; (7) Finally, despite pooling, the reported confidence intervals are still wide, especially for the efficacy of low versus standard doses. Large differences between the treatments are still possible, and thus it cannot be concluded that low and standard doses have equivalent efficacy.

Again, a dose-response relationship for adverse effects and dropout due to adverse effects was found,¹ emphasising the need to define an *optimal* dose. SSRIs are tolerated better than TCAs (without differentiation of doses used).^{2,3} Furukawa *et al* cite a Canadian meta-analysis that found comparable efficacy of standard-dose SSRIs versus low or standard dose TCAs.⁴ The relative tolerability of these medications was not reported. Another review is currently underway to assess dose-response relationships for antidepressants.⁵ Higher doses are likely to be accompanied by more disturbing adverse effects, increasing the risk of intolerability. The balance between efficacy and tolerability needs to be continually discussed with patients in order to make a collaborative decision about the dosages used at consecutive time-points.

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- 1 Bollini P, Pampallona S, Tibaldi G *et al*. Effectiveness of antidepressants. Meta-analysis of dose-effect relationships in randomised clinical trials. *Br J Psychiatry* 1999;174: 297-303.
- 2 Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* 1995; 310: 1433-8.
- 3 Barbui C, Hotopf M, Freemantle N *et al*. Treatment discontinuation with selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs) (Cochrane Review). *Cochrane Library*, Issue 4. Oxford: Update Software, 2002.
- 4 Trindade E, Menon D. *Selective serotonin reuptake inhibitors (SSRIs) for major depression. Part 1: Evaluation of the clinical literature (report 3E)*. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 1997.
- 5 Ruhé HG, Huyser J, Scholten RJP *et al*. Initial high dose versus standard dose of antidepressants for depression (Protocol for a Cochrane Review). *Cochrane Library*, Issue 1. Oxford: Update Software, 2003.