

Review: Antidepressants improve headache in patients with chronic headache

Tomkins GE, Jackson JL, O'Malley PG, Balden E, Santoro JE. Treatment of chronic headache with antidepressants: a meta-analysis. *Am J Med.* 2001 Jul;111:54-63.

QUESTION

In patients with chronic headache, how effective are antidepressants?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 to December 1998), PsycLIT (1974 to December 1998), EMBASE/Excerpta Medica (1974 to December 1998), and the Cochrane Library. Bibliographies of relevant articles were reviewed, and Federal Research in Progress was searched for information on unpublished trials.

STUDY SELECTION

Studies in any language were selected if they were randomized controlled trials (RCTs) comparing the effectiveness of antidepressants with placebo in patients with chronic headache and if measurable outcomes were reported.

DATA EXTRACTION

Data were extracted on setting, country of origin, patient inclusion and exclusion criteria, sample size, demographic characteristics, comorbid psychiatric disease, concurrent use of analgesic medications, key components of the intervention, study quality, adverse

effects, and outcomes. Outcomes were overall improvement in headache (> 50% reduction in Headache Index scores, global improvement based on > 50% improvement, impression of improvement, or headache frequency or severity) and effect size of treatment (measured in standard deviation units) on headache burden.

MAIN RESULTS

38 RCTs met the selection criteria. Interventions included tricyclic antidepressants (TCAs) (19 RCTs), serotonin-blocking agents (18 RCTs), and selective serotonin-reuptake inhibitors (SSRIs) (7 RCTs). The rate of overall improvement in headache was greater in the treatment group than the placebo group ($P < 0.05$) (Table). Improvement in headache burden (measured by effect size of treatment) was greater in the

treatment group than the placebo group (standardized mean difference [SMD] 0.94, 95% CI 0.64 to 1.12). Consumption of analgesic medication (measured by effect size of treatment) was lower in the treatment group than the placebo group (SMD -0.7, CI -0.9 to -0.5). Outcomes did not differ by type of headache (migraine vs tension) or by category of antidepressant.

CONCLUSION

In patients with chronic headache, treatment with antidepressants is associated with overall improvement in headache, and improvement in headache burden.

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Antidepressants vs placebo for chronic headache*

Outcome at 4 to 27 wk	Weighted event rates†		RBI (95% CI)	NNT (CI)
	Antidepressants	Placebo		
Overall improvement	65%	33%	100% (60 to 140)	4 (3 to 5)

*Meta-analyses were done using a random-effects model. Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

†Information provided by author.

COMMENTARY

The meta-analysis by Tomkins and colleagues concludes that 1 in 3 patients with chronic headaches benefits from antidepressants. The effect is independent of headache type (migraine or tension) and drug class (TCAs, serotonin receptor antagonists, or SSRIs), with the possible exception that SSRIs are not as well studied and may be less effective. The effect seems independent of the presence of depression, but studies are inconsistent.

The results of Tomkins and colleagues are consistent with those of other systematic reviews (1, 2) and indicate that antidepressants, especially TCAs, are a reasonable first choice to treat headaches. The choice of therapy depends on the patient's comorbid illnesses that might be improved or worsened by the treatment for headache.

The authors' thorough analysis shows problems in the published studies. First, the authors found statistically significant heterogeneity among the studies with a 4-fold variation in rate ratios. This finding is not surprising given the range of drugs and patients. Second, the authors found statistical evidence of publication bias. Although unpublished studies will probably not reverse the results of this meta-analysis, unpublished negative studies will probably lessen the degree of benefit.

Two types of studies are now needed. First, we need larger studies to reduce the effect of publication bias and allow effective analysis of the

true benefits and variation in results. Second, we need comparisons of antidepressants with other therapies and combinations of therapy. One study published since the meta-analysis by Tomkins and colleagues was written meets these criteria: Holroyd and colleagues (3) compared TCAs with stress management therapy and placebo in 233 patients with tension headaches (almost twice the size of the largest trial in this meta-analysis). 38% of patients benefited from TCAs (less than in the current analysis), whereas combined therapy benefited 64% of patients (3).

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References

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3. Holroyd KA, O'Donnell FJ, Stensland M, et al. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA.* 2001;285:2208-15.