Tricyclic antidepressants for migraine and tension-type headaches

Are largely beneficial, but a lack of research leaves important clinical questions unanswered

Kenneth A Holroyd distinguished professor¹, Lars Bendtsen associate professor²

¹Department of Psychology, Ohio University, Athens, OH 45701, USA; ²Danish Headache Centre, Department of Neurology, University of Copenhagen, Glostrup Hospital, DK-2600 Glostrup, Denmark

In the linked meta-analysis (doi:10.1136/bmj.c5222), Jackson and colleagues assess the efficacy of tricyclic antidepressants in the treatment of migraine, tension headache, and mixed headache.¹

Tricyclic antidepressants have a long history in the treatment of headache. In 1964 Lance and Curran reported a better response to amitriptyline (30-75 mg/day) in chronic tension headache (n=280) compared with 11 other commonly used drugs (such as benzodiazepines, vasodilators, and sedatives).² They also reported a placebo controlled crossover trial of 27 patients that showed clinically significant improvements (≥50% reduction) in headaches in 55% of patients taking amitriptyline, but only 11% of those taking placebo. When the results for amitriptyline were aggregated across the two studies, the effect of amitriptyline became more pronounced over time, was independent of the presence of depression, was evident in patients with continuous as well as episodic headaches, and was most pronounced in older (≥60 year of age) patients. A decade passed before similar positive findings were reported for migraine.³

With replication of these findings tricyclic antidepressants, particularly amitriptyline, have been recommended in textbooks for at least 35 years. With the advent of formal treatment guidelines for headache, tricyclics also have been recommended in clinical guidelines for the treatment of tension-type headache and migraine.⁴⁵

The current meta-analysis updates the evidence base for tricyclic antidepressants in the treatment of migraine and tension headache.⁶ Results from the 37 trials of tricyclic antidepressants are analysed; the 20 placebo controlled trials primarily evaluate amitriptyline (14 trials) or clomipramine (four trials). The meta-analysis largely confirms Lance and Curran’s original observations. Across trials, low dose tricyclic antidepressants (mean amitriptyline dose 80 mg/day) reduced headache by at least 50% compared with placebo (tension: relative risk 1.41, 95% confidence interval 1.02 to 1.89; migraine: 1.80, 1.24 to 2.62). The proportion of people who stopped treatment did not differ significantly between people taking tricyclic antidepressants or placebo. Treatment effects increased over time. Other preventive drugs (topiramate or β blockers) showed no advantage over tricyclic antidepressants. Tricyclic antidepressants were significantly more effective than serotonin reuptake inhibitors (tension (four trials): 1.73, 1.34 to 2.22; migraine (five trials): 1.72, 1.15 to 2.55), although dry mouth, drowsiness, and weight gain were also significantly more common with tricyclics.

Conclusions that can be drawn from meta-analyses depend on the number and quality of available trials. As the authors rightly point out, the number of studies was not large and most were small and of short duration (average 11 weeks). Moreover, most trials would not meet current methodological standards because 80% (16/20) of placebo controlled trials were completed at least 20 years ago.⁷ As a result, convincing evidence is available for only the most general conclusion: amitriptyline is more effective than placebo for migraine and tension headache. Amitriptyline also seems to be more effective than serotonin reuptake inhibitors, although few direct comparisons are available.

After a half century of research the most important clinical questions remain unanswered. Is the observed effect of amitriptyline a true class effect of tricyclic antidepressants or specific to a subset of tricyclics? Are newer selective dual action
(serotonin and noradrenaline) antidepressants as effective as tricyclic antidepressants with, potentially, a more favourable side effect profile? How does the effectiveness of tricyclic antidepressants compare with other preventive drugs or with non-drug treatments? Which people are the best candidates for tricyclic antidepressants rather than other preventive drugs or non-drug treatments? Can tricyclic antidepressants be beneficially combined with other preventive drugs or non-drug treatments in people who do not respond to monotherapy? Secondary analyses of available clinical trial data can yield answers to some of these questions. However, just a few large properly designed trials might answer many of these questions, as well as other clinically relevant questions. Unfortunately, a 50 year history indicates that such trials will not be conducted. Incentives are too few and disincentives too substantial for the drug industry to conduct such trials. The establishment of a combination of incentives and requirements to encourage the industry to provide information about comparative effectiveness and other clinically relevant questions during premarket approval or postmarket research is unlikely to occur. Thus, support from government health agencies or from other healthcare players with an interest in identifying cost effective treatments will be needed in addition to existing examples of government funded trials.

Competing interests: Both authors have completed the Unified Competing Interest form at www.icmje.org/coiDisclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work. KAH has received support from the National Institutes of Health (NINDS; NS32375). LB declares no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; both authors declare no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Jackson JL, Shimeall W, Seccesss L, DeZee KJ, Bocher D, Dinsier M, et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. BMJ 2010;341:c5222.
2 Lancos JW, Curran DA. Treatment of chronic tension headache. Lancet 1964;1:1236-9.
3 Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. J Neurol Neurosurg Psychiatry 1973;36:684-90
4 Evers S, Afta J, Frase A, Goadsby P, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine - revised report of an EFNS task force. Eur J Neurol 2009;16:968-81.
5 Bendtsen L, Evers S, Linde M, Miktoskaa DD, Sandrinii G, Sibweeney J. EFNS guideline on the treatment of tension-type headache—report of an EFNS task force. Eur J Neurol 2010; published online 11 May.
6 Ramadan N, Silberstein S, Freitag F, Gilbert T, Friborg B. Evidence-based guidelines for migraine headache in the primary care setting; pharmacological management for the prevention of migraine. American Academy of Neurology Guidelines, 2002. www.aan.com/professionals/practice/pdfs/g0090.pdf.
7 Bendtsen L, Bigal M, Cerbo R, Diner H, Holroyd, Lampl C, et al. Guidelines for controlled trials of drugs in tension-type headache: second edition. Cephalalgia 2010;30:1-16.
8 Thli-Hansen P, Block G, DahlØ C, Diner H-C, Ferrarni M, Goadsby P, et al. Guidelines for controlled trials of drugs in migraine: second edition. Cephalalgia 2000;20:765-86.
9 Holroyd K, Labus L, Carlson B. Moderation and mediation in the psychological and drug treatment of chronic tension type headache: the role of disorder severity and psychiatric comorbidity. Pain 2009;143:213-22.
10 Holroyd KA, O’Donnell FJ, Stenland M, Lpchik GL, Cordingley GE, Carlson B. 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.
11 National Institutes of Health, NINDS Clinical Research Center. Chronic Migraine Treatment Trial. www.ninds.nih.gov/disorders/clinical_trials/NCIT00772031.htm.

Cite this as: BMJ 2010;341:c5250

Related links

bmj.com archive

Research

• Effect of preventive (β blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine (BMJ 2010;341:c4871)

Practice

• Diagnosis and management of headache in adults: summary of SIGN guideline (BMJ 2008;337:a2329)

© BMJ Publishing Group Ltd 2010