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## Antidepressants in the treatment of chronic headaches: therapy of psychiatric comorbidity or other mechanisms?

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**Abstract** Antidepressants are often used in the prophylaxis of chronic headaches, but their effectiveness is uncertain. A recent meta-analysis showed that antidepressants are effective in the treatment of chronic headaches. Double-blind, placebo-controlled studies showed that amitriptyline and fluoxetine may be useful in the prophylaxis of chronic headaches. Further studies are needed in order to evaluate whether

there are differences in efficacy among the classes of agents and whether this effect is independent of depression treatment.

**Key words** Chronic headaches • Antidepressants • Meta-analysis • TCAs • SSRI

Chronic daily headache (CDH) affects approximately 4%–5% of the population and encompasses a number of different diagnoses, including transformed migraine, chronic tension-type headache, new-onset daily persistent headache, and hemicrania continua [1]. The goals of prophylactic therapy in chronic headaches are (a) to reduce the frequency, severity, and duration of headache attacks; (b) to improve responsiveness to treatment of acute attacks; (c) to improve function; and (d) to reduce disability. Several pharmacologic treatment options for chronic headaches exist, including serotonin agonists, ergots, antidepressants, anti-convulsants, muscle relaxants, serotonin antagonists, antianxiety agents, and other miscellaneous drugs. Major depression and migraine are commonly comorbid and, therefore, antidepressants are often used to prevent chronic headache, but their effectiveness is uncertain.

To evaluate the usefulness of antidepressants in the prophylactic treatment of chronic headaches, a meta-analysis of English-language, randomized placebo-controlled trials was recently performed [2]. Thirty-eight tri-

als were included in the study. Twenty-five studies focused on migraines, 12 on tension headaches, and 1 on both entities. Of these studies, 19 used tricyclic antidepressants, 18 serotonin antagonists, and 7 selective serotonin reuptake inhibitors. Patients receiving antidepressants were twice as likely to report headache reduction. The average amount of reduction was 0.94 (95% CI: 0.65–1.2), an effect considered large. Treated patients also consumed less analgesic medication. There were no differences in outcomes among the three classes of agents studied or among the type of headache (migraine vs. tension), quality score, length of treatment, or percentage of patients lost to follow-up. Thus, the authors concluded that antidepressants are effective in preventing chronic headaches.

*Tricyclic antidepressants (TCAs)* are a mainstay in the prophylactic therapy of migraine and chronic tension-type headache. *Amitriptyline*, *nortriptyline*, *clomipramine*, and *doxepin* have been the major agents for prophylactic treatment of migraine. Amitriptyline has been more frequently

studied than the other agents and is the only antidepressant with fairly consistent support for effectiveness in headache prevention. Three placebo-controlled trials found amitriptyline significantly better than placebo at reducing headache index or frequency [3–5]. A trial reported that amitriptyline was significantly more efficacious than propranolol for patients with mixed migraine and tension-type headache [6]. The mechanism of action of amitriptyline in headache prevention is unknown but does not result from treating depression. Recent studies provided evidence that TCAs increase the activity of the membrane steroid transporters that regulates access of glucocorticoids to the brain [7]. In addition, TCAs inhibit NMDA receptors and small-conductance, calcium-activated K<sup>+</sup> channels [8]. The clinical use of amitriptyline, however, is often limited by the large number of anticholinergic side effects. The high-affinity selective serotonin reuptake inhibitors (SSRIs) have recently been used in the prophylactic treatment of migraine and tension-type headache. *Fluoxetine* appeared to be a safe and effective drug for headache prophylaxis. A recent randomized, double-blind, parallel study in patients with migraine showed that fluoxetine (20 mg daily) induces a significant reduction of total pain index beginning from the 3rd month of treatment [9]. Adverse events are generally less common in headache patients treated with SSRIs than with TCAs, with nausea and sexual dysfunction being the most frequently reported symptoms. A recent study compared the effectiveness of amitriptyline and of the selective serotonin reuptake inhibitor *citalo-*

*pram* in chronic tension-type headache [10]. Forty non-depressed patients with chronic tension-type headache were included in a 32-week, double-blind, placebo-controlled study. Amitriptyline reduced the area under the headache curve by 30% compared with placebo ( $p=0.002$ ), whereas citalopram had no significant effect ( $p=0.68$ ). Explanatory analyses showed that amitriptyline significantly reduced the duration of headache ( $p=0.01$ ), headache frequency ( $p=0.01$ ), and intake of analgesics ( $p=0.02$ ) but not headache intensity ( $p=0.12$ ). Although amitriptyline did not eliminate the headache, it provided a clinically important reduction of headache in the majority of otherwise treatment-resistant patients. The differential effect of amitriptyline and citalopram indicates that mechanisms other than inhibition of serotonin reuptake are involved in the analgesic effect of the tricyclic antidepressants. At present, the evidence supporting the use of atypical antidepressants, such as *mianserin*, *fluvoxamine*, *venlafaxine*, and *mirtazapine*, in the prevention of chronic headaches is insufficient.

In conclusion, several studies showed that antidepressant therapy is effective in the prophylaxis of chronic headaches. The benefit is moderate to large in amplitude. Additional studies are needed to evaluate whether there are differences in effectiveness among the classes of agents. Finally, studies that determine whether particular migraine patient subgroups are more likely to respond to antidepressant therapy, such as depressed patients or those with high analgesic use, are necessary.

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