The Use of Antidepressants for Headache Prophylaxis

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SUMMARY

The focus of this review is on the efficacy of antidepressants as preventive treatments for migraine and chronic tension-type headache (TTH). Pharmacologic prophylaxis may be indicated for patients with frequent headaches, who respond insufficiently to acute therapies, or for whom medication overuse is a concern. The well-documented efficacy of the tricyclic antidepressant amitriptyline, both for migraine and chronic TTH, has been followed by widespread use of other antidepressants for headache prophylaxis. Although antidepressants in general share comparable efficacy for the treatment of depressive disorders, their efficacy as headache preventives varies widely. Evidence supporting use of the selective serotonin reuptake inhibitors as headache preventives is poor; their use should be reserved for treating comorbid depression in a patient who also has a headache disorder. Small randomized trials of venlafaxine indicate preliminary efficacy both for migraine and tension-type headache. Evidence for other antidepressants is lacking. Although antidepressants are often prescribed to headache patients under the assumption that the prescribed agent also will be effective in reducing symptoms of comorbid depression, the majority of studies have failed to find a strong relationship between depression symptoms and headache improvement. Suggestions for future research are discussed.

Introduction

Migraine and tension-type headaches are the two most common headache conditions and cause significant suffering and functional impairment for millions of individuals each year. Migraine is now conceptualized as a chronic disorder with episodic manifestations that may persist or progress in frequency over time as a function of biologic, psychologic, and environmental influences [1]. Although typically less disabling than migraine, tension-type headache (TTH) is even more prevalent in the general population (38% yearly prevalence) [2] and has significant impact when it occurs frequently. Patients with infrequent migraine or episodic TTH often achieve adequate control with acute pharmacologic treatment, and the migraine-specific selective serotonin agonists (triptans) have indeed revolutionized the abortive treatment of migraine. However, for patients with frequent headaches, those who respond insufficiently to acute therapies, or those for whom overuse of acute med-

ication is a concern, preventive therapies may be indicated.

All major categories of preventive pharmacologic therapies for migraine and tension-type headache (β -blockers, calcium channel blockers, antiepileptics, and antidepressants) were initially developed for another medical indication rather than based on knowledge of migraine pathophysiology [3]. The use of antidepressants for headache prophylaxis was guided initially by serendipitous discoveries and assumptions about shared mechanisms of action. The majority of antidepressants demonstrate comparable efficacy for the treatment of depression [4–6], the choice among which often is dictated by side effect profiles, symptomatology patterns, prior treatment response, and concurrent medications. However, their efficacy for chronic pain and headache disorders varies considerably.

The focus of this review is on the efficacy and use of antidepressant medications as headache preventives for both migraine and chronic TTH. We begin by overviewing

the pathophysiology of headache, because similar neurotransmitters underlie both migraine and mood disorders and because an understanding of headache pathophysiology informs treatment decisions. The majority of the review focuses on the efficacy of specific antidepressants for migraine and tension-type headache, followed by discussion of the role of comorbid psychopathology as it relates to prescribing antidepressants for headache patients. The review closes with a discussion of areas for future research.

This narrative review was informed primarily by a review of previous meta-analytic studies and systematic reviews that examined the use of antidepressants for migraine and TTH prophylaxis. Trials on this topic published since the end search date of the most recent review (September 2008) were searched for using PubMed and PsycINFO (September 2008 to November 2009) keyword parameters that included the words “headache,” “migraine,” or “tension-type headache” and either “antidepressant” or a specific type of antidepressant. Trials on antidepressants excluded from most prior reviews (e.g., serotonin/norepinephrine reuptake inhibitors [SNRIs]) were located using a similar strategy that excluded the date specifications.

Pathophysiology of Migraine

Advances in functional neuroimaging have revolutionized our understanding of migraine. Once thought to be primarily vasculogenic resulting from constriction and subsequent dilation of cerebral blood vessels, migraine is now understood to be primarily neurogenic, and the observed vascular phenomena are secondary or epiphenomena to an underlying disturbance of the central nervous system (the trigeminovascular system in particular). As allodynia is a well-recognized aspect of migraine, migraine may be considered a process of dysmodulation of normal pain control. However, migraine also involves multisensory disturbances related to light, sound, and smell. Thus, migraine was recently described as “. . . an inherited dysfunction of sensory modulatory networks with the dominant disturbance affecting abnormal processing of essentially normal traffic” [7, p. 327].

A putative “migraine generator” has been identified as an area in the brainstem that includes key centers of neuromodulation: the locus coeruleus (center of noreadrenergic control), dorsal raphe nucleus (center of serotonergic control), and periaqueductal gray (involved in pain modulation). A migraine attack presumably is triggered when a stimulus (an external trigger such as a food or an internal change in homeostasis) stimulates this brainstem region, which sends output through the sev-

enth cranial nerve (sphenopalatine ganglion) to trigger dilation of meningeal blood vessels and release of neuroinflammatory compounds. These neuroinflammatory compounds trigger further blood vessel dilation and neuronal signals that feed back to the trigeminal nucleus caudalis (the sensory nucleus of the head and upper neck) to generate the migraine process.

Pain transmission in the central nervous system is influenced by a wide range of neurotransmitters, including norepinephrine, dopamine, serotonin, γ -aminobutyric acid (GABA), and enkephalins/endorphins. Increases in norepinephrine and dopamine have a migraine-provoking effect, whereas activation of other neurotransmitter receptors serves to inhibit migraine activity. Interestingly, many of these same neurotransmitters are critically involved in mood and other emotional states, supporting a biological basis for comorbidity between migraine and mood disorders [8]. Serotonin is perhaps the best exemplar, as chronically low serotonergic availability can predispose one to cortical spreading depression and increase sensitivity of trigeminovascular pathways that underlie migraine pain [9]. Both migraine and depression appear related to a reduced serotonergic disposition, and the efficacy of medications that increase central serotonin levels (triptans) offers indirect evidence for a shared serotonergic dysfunction.

Efficacy of Specific Antidepressants

Tricyclic Antidepressants

The tricyclic antidepressant amitriptyline has been the most studied headache prophylactic. Placebo-controlled trials have found that amitriptyline treatment results in lower scores on headache indices than placebo treatment for both migraine [10–14] and chronic TTH patients [15–19]. The three controlled studies of amitriptyline for TTH included in the meta-analysis by McCrory *et al.* [20] yielded, on average, a 33% reduction in headache activity. Amitriptyline also is efficacious for patients with “mixed” migraine and TTH [21–23]. In comparison trials, amitriptyline has produced mixed results when compared to the β -blocker propranolol [13,14,23] but typically has outperformed the SSRIs [15,24,25]. The 2000 Evidence-Based Guidelines for migraine prevention [26], endorsed by the U.S. Headache Consortium and American Academy of Neurology, designated amitriptyline as a first-line treatment for the prevention of migraine (Grade A evidence, Group 1 recommendation). Amitriptyline was the only antidepressant of any kind to receive this designation.

Other tricyclics have been studied far less frequently than amitriptyline and do not share the same strength

of efficacy for either migraine or chronic TTH [26]. Their use is based primarily on clinical experience, although some positive findings in uncontrolled or small trials have been reported for protriptyline [27], doxepin [28], and imipramine [29]. Although there are no specific clinical trials of nortriptyline, it is the active metabolite of amitriptyline and may be preferred because it is less sedating and may cause less weight gain. Clomipramine is not indicated because of its poor efficacy and high rates of adverse events [30,31]. Tricyclics are sometimes poorly tolerated by patients because of their anticholinergic and antihistaminic side effects, including sedation. Because of its sedating effects, amitriptyline may be especially useful for headache patients with insomnia. Amitriptyline has a wide effective dose range, and patients with comorbid major depression typically require higher doses than those with headache alone. Amitriptyline should be administered at bedtime and the dose increased gradually, beginning at 10–25 mg [32]. The usual effective dose for headache prevention is 50–75 mg, lower than doses used for antidepressant effect. In addition to those with medical contraindications, amitriptyline may not be an appropriate treatment choice for some elderly patients or those at high risk for suicide (due to toxicity in overdose).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Because of their favorable side effect profiles and relatively low toxicity, SSRIs are the most commonly prescribed class of antidepressant for the treatment of depression. However, evidence supporting their use as headache preventives is poor. Most existing studies have not been randomized controlled trials or have had methodological shortcomings that limit their validity (e.g., not double-blinded, short duration of follow-up, failure to include intention-to-treat analyses). A 2005 meta-analytic Cochrane review provided the most comprehensive assessment of the efficacy of SSRIs for headache prevention [24]. This review identified 13 trials comparing five SSRIs to other antidepressants, with fluoxetine being most frequently studied. These 13 trials compared 636 participants (38.5% migraine, 42.6% chronic TTH). Mean difference comparisons of headache index scores at 2-month follow-up indicated that the various SSRIs were no better than placebo for treatment of migraine. For chronic TTH, SSRIs were equivalent to placebo and less effective than tricyclics (typically amitriptyline) in reducing headache duration and analgesic use. Minor side effects were less common with SSRIs than tricyclics, but the frequency of side effects had no effect on dropout rates.

An older meta-analysis that compared 38 randomized, placebo-controlled trials of antidepressants for mi-

graine and TTH found that tricyclics, serotonin antagonists (e.g., pizotifen, mianserin), and SSRIs did not differ statistically in their efficacy (standard mean difference = 0.94) [33]. However, only four arms of these 38 studies included SSRIs in production today (fluoxetine, fluvoxamine, citalopram), and the majority of SSRI studies that were included found no significant effects. The U.S. Headache Consortium Guidelines [26] concluded that fluoxetine was modestly effective for the prevention of migraine, while qualifying that the strength of evidence was less than optimal (Grade B evidence, Group 2 recommendation). By comparison, reported efficacy of the other SSRIs was limited to clinical experience and consensus rather than scientific evidence. Reviews published since the Evidence-Based Guidelines have concluded that SSRIs have demonstrated generally poor efficacy for headache prevention, while acknowledging significant methodological limitations in this literature [34–37].

Considered together, existing literature provides weak support for the routine use of SSRIs in preventing migraine and chronic TTH. Fluoxetine is the only widely used SSRI that has been studied with any significant frequency, and most positive studies of fluoxetine have suffered from significant methodological weaknesses [34]. SSRIs do have lower rates of adverse effects than the tricyclics, but this benefit does not always translate into better adherence. SSRIs may be an appropriate augmentive therapy for individuals who have comorbid depression that does not respond to amitriptyline alone.

Other Antidepressants

Although they have not been studied as frequently as the tricyclics or SSRIs, serotonin antagonists, monoamine oxidase inhibitors (MAOIs), and SNRIs also have been evaluated as headache prophylactics. Serotonin antagonists (e.g., pizotifen, mianserin) have received some support for reducing headache frequency and headache burden [33] but are not used frequently because of their side effect profiles. MAOIs are used infrequently for headache prophylaxis due to required dietary restrictions, side effects, and drug interactions. Phenelzine is the MAOI most commonly used for headache prevention, but its reported efficacy is limited to clinical consensus rather than scientific evidence [26]. Randomized trials of venlafaxine, both for migraine [38,39] and TTH [40], have provided preliminary evidence that this agent is effective in reducing headache frequency and may be better tolerated than amitriptyline [38].

Open-label and retrospective studies have provided conflicting results regarding the efficacy of duloxetine [41,42]. A small, double-blind trial suggested that

mirtazapine might be beneficial for chronic TTH patients who have failed numerous other treatments [43]. However, neither of these agents has been evaluated sufficiently.

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening acute reaction that can develop in individuals taking agents that increase serotonergic activity. Signs and symptoms typically include cognitive (mental status changes, confusion, agitation), autonomic (shivering, sweating, fever, diarrhea, tachycardia), and somatic (myoclonus, hyperreflexia, tremor) manifestations that often develop within a few hours of beginning a new drug regimen. Although most commonly discussed in relation to individuals prescribed a triptan and an SSRI, serotonin syndrome also can occur in individuals taking other serotonergic agents such as tricyclics, MAOIs, and lithium. Prescribing physicians should be attentive to drug interactions when considering antidepressant pharmacotherapy for headache patients, specifically being mindful of serotonin syndrome in individuals prescribed multiple serotonergic agents. Despite the caution issued by the U.S. Food and Drug Administration, the actual risk of serotonin syndrome in individuals taking a triptan and an SSRI appears quite low [25,44,45]. The large majority of individuals tolerate triptan/SSRI combination therapy well, and the rare exceptions typically develop only mild to moderate symptoms that remit when one of the agents is discontinued [44].

Combining Antidepressants with Behavioral Treatments

The principle that behavioral therapy may be combined with preventive drug therapy to achieve added clinical improvement in the management of primary headache disorders is widely accepted [26,46,47]. The empirical evidence in support of this claim is consistent but limited. The best available evidence addressing this issue was produced by Holroyd *et al.* [48], who randomly assigned over 200 chronic TTH patients to the following conditions: tricyclic antidepressant alone, stress-management training alone, combined antidepressant and stress-management training, or medication placebo. When used alone, antidepressants and stress-management training each yielded greater improvements than placebo with respect to headache activity, analgesic medication use, and disability. However, the combined therapy was more likely to produce clinically meaningful reductions in headache (64% of patients) than either antidepressant (38%) or stress management training (35%)

alone. This study clearly demonstrated that the combination of both treatment strategies yielded the greatest benefit, whereas each strategy alone was only modestly effective.

Impact of Comorbid Depression and Anxiety

Migraine and chronic TTH patients are between two and five times more likely to suffer from a depressive or anxiety disorder than are individuals without headache [49–52]. Psychiatric comorbidities are particularly common among those with chronic headache forms and those who present to clinic settings. As such, comorbid psychopathology has been implicated as a risk factor contributing to the progression (chronification) of headache over time, although the responsible mechanisms remain largely unclear [53].

Antidepressants often are prescribed to headache patients under the assumption that the prescribed agent also will be effective in reducing symptoms of comorbid depression or anxiety. Despite this rationale and the prevalence of psychiatric comorbidities among headache patients, less than half of the trials using antidepressants for prevention of migraine or TTH have assessed the relationship between comorbid depression and headache. Most have failed to compare psychiatric subgroups or have excluded patients with psychiatric disorders altogether, as is the case with the major trials on venlafaxine conducted over the last several years [38–40]. Assessment of anxiety symptoms is particularly rare.

Studies of amitriptyline and SSRIs that have included assessment of depression symptoms have obtained conflicting results. Some have found that antidepressant treatment improved depression symptoms in headache patients [25,54,55]; others have reported that headache improvement with these agents is independent of or weakly related to comorbid depression or anxiety [13,56]. In total, the majority of studies that have assessed comorbid depression symptoms have found no relationship between depression and headache improvement, with most remaining studies finding only weak correlations between these two variables ($r_s = 0.1\text{--}0.3$) [33]. Whether this pattern of results holds true for the SNRIs is unknown. One open-label trial suggested that duloxetine might improve comorbid depression and headache [42], but a retrospective study of duloxetine showed only a 22% responder rate (defined as 50% reduction in headache days), with little change whether there was comorbid anxiety or depression [41].

The notion that antidepressants impact headache by treating an underlying depression is thus largely untenable, because (1) most studies have found weak to

no relation between depressive symptoms and headache improvement, (2) existing studies have included many nondepressed headache patients, and (3) most studies have used doses and treatment durations that are often insufficient to treat depression.

The mechanisms of action that underlie the antinociceptive action of some antidepressants remain speculative. The superior efficacy of amitriptyline as compared to the SSRIs, and the potential promise of venlafaxine, suggest that inhibition of serotonin reuptake alone may be insufficient for headache improvement and that selective noradrenergic action of some kind (e.g., norepinephrine reuptake inhibition) may be required. Consistent with the chronic pain literature, it appears that agents with mixed noradrenergic and serotonergic properties are most effective. Further research is needed to ascertain the mechanisms that underlie the effectiveness of some antidepressants on migraine and TTH.

Previously, clinicians often attempted to treat comorbid headache and depression using a single antidepressant. However, because adjusting a single drug to meet the dosing requirements of two conditions often proves difficult, clinical practice more often favors treating each disorder with an agent specific to the disorder. One strategy is to augment a prophylactic headache agent with an antidepressant [35]. Although antidepressants frequently are prescribed to treat anxiety disorders, no conclusive statement can be made regarding their use for treating comorbid anxiety in headache patients. Use of some antidepressants in bipolar patients with headache may be contraindicated due to the risk of inducing mania.

Future Directions

Because many of the studies reviewed here suffer from methodological weaknesses, we offer the following suggestions for future research:

1. *Routinely assess for and include patients with comorbid psychopathology.* This may be accomplished through the use of well-validated self-report and/or interview measures appropriate for headache patients [57], both as inclusion criteria and outcome measures. Such trials should evaluate a range of doses, incorporate longer periods of treatment, and extend the follow-up period to at least 6 months.
2. *Endeavor to match treatments to patient subgroups.* Future studies should attempt to determine the subgroups of patients for whom a particular antidepressant treatment or treatment combination is most effective (e.g., episodic vs. chronic migraine, depressed vs. nondepressed, those with high frequency of analgesic use, those who have responded poorly to other specific agents).
3. *Incorporate revised ICHD-2 diagnostic criteria.* Many studies comprising this review, particularly those on amitriptyline, were conducted prior to the publication of the revised diagnostic criteria specified by the International Headache Society [58]. Revisions to diagnostic criteria mandate replication of older studies among clearly defined patient groups that include chronic and episodic headache subforms. Use of a structured headache interview and headache diary can facilitate participant inclusion that is based on the revised diagnostic criteria.
4. *Improve methodological rigor.* Future studies on specific antidepressants should extend the follow-up period to at least 6 months, include intention-to-treat analyses to facilitate interpretation of data from study attrition, and incorporate standard headache outcome measures. At a minimum, this should include some measure of headache frequency derived from daily headache self-reports consistent with the International Headache Society guidelines for controlled trials of drug treatments [59,60]. Measures of headache intensity/severity, headache duration, frequency of acute medication use, headache-related disability, and quality-of-life metrics are recommended as additional outcome variables.

Conclusion

Amitriptyline is the only antidepressant that has yielded consistent evidence of efficacy for the treatment of migraine and chronic TTH. However, an unfavorable side effect profile limits its use as a first-line preventive. Nortriptyline is the active metabolite of amitriptyline and is commonly used, although this agent has not been studied as a headache preventive. The lack of evidence of efficacy for the SSRIs suggests that their use should be limited to the treatment of depression or anxiety in the headache patient, but not primarily as headache preventives. Three small but randomized trials have shown preliminary evidence of efficacy for venlafaxine. At present there is no convincing evidence for the SNRI duloxetine. Although some studies have observed a relationship between depression symptoms and headache improvement during antidepressant therapy, the majority of studies have failed to find evidence of a strong relationship between these variables. Most studies have not assessed depression or anxiety symptoms during treatment or have excluded patients with psychiatric comorbidities.

Author Contributions

Each author contributed through acquisition and interpretation of relevant literature, drafting and revising portions of the paper, and approving the final version.

Disclosures

Dr. Maizels has served on the advisory boards for MAP Pharmaceuticals and Zogenix within the past year. Dr. Penzien has consulted for MAP Pharmaceuticals and Endo Pharmaceuticals within the past year.

Conflict of Interest

The authors declare no conflict of interest.

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