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Headache (JR Couch, Section Editor)

Antidepressants for Preventive Treatment of Migraine

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Key Points

- Drugs with combined serotonergic and noradrenergic effects have better anti-nociceptive efficacy than drugs that affect serotonin alone.
- Amitriptyline has the best evidence for use in migraine prevention, with level B evidence in multiple treatment guidelines. Nortriptyline is the most common alternative TCA.
- The sedating effect of TCAs can be beneficial for patients with comorbid insomnia.
- SNRIs including venlafaxine and duloxetine also have good evidence for efficacy and may be the most effective treatments in patients with comorbid depression and migraine. Patients should be counseled about the possibility of a withdrawal effect from SNRIs.
- SSRIs including fluoxetine are not effective for most patients and are infrequently used.

This article is part of the Topical Collection on *Headache*

Keywords Antidepressants · SSRI · SNRI · TCA · Migraine · Prevention · Treatment

Abstract

Purpose of review This review describes the pharmacology of each antidepressant class as it applies to migraine prevention, summarizes the evidence base for each medication, and describes relevant side effects and clinical considerations. Use of antidepressants for migraine prevention in clinical practice is also discussed.
Recent findings Antidepressants are commonly used as migraine preventives. Amitriptyline has the best evidence for use in migraine prevention. Nortriptyline is an alternative in patients who may not tolerate amitriptyline. The sedating effect of TCAs can be beneficial for patients with comorbid insomnia. SNRIs including venlafaxine and duloxetine also have evidence for efficacy and may be the most effective treatments in patients with comorbid depression and migraine. SSRIs including fluoxetine are not effective for most patients. The side effect burden of antidepressants can be substantial. Patients should be particularly counseled about the possibility of a withdrawal effect from SNRIs.
Summary Antidepressants are an important option for preventive treatment of migraine. Further research on the efficacy and tolerability of SNRIs as migraine preventives is needed.

Introduction

Migraine is a recurrent, disabling neurovascular condition that affects about 15% of the US population [1]. It is more common in females than males, with a prevalence ratio of about 2:1. The disability associated with migraine can be significant, with disability affecting both home and work activities [2]. The most typical pattern of migraine is characterized by episodic attacks with periods of symptom freedom between migraines [3]. If attacks occur less than 4 days a month and are not debilitating, they may be managed solely with abortive treatment, such as a triptan. If headaches become more frequent, preventive treatment may be necessary [4]. The

Table 1. Antidepressants with evidence for use in migraine prevention

Name	Dose/frequency	AAN/AHS evidence level	Common side effects	Notes
TCAs:				
Amitriptyline	25–50 mg daily (clinical experience supports starting at 10 mg daily; clinical trials included doses up to 100 mg daily; dose as needed for effect and as tolerated)	Level B	Sedation, weight gain, dry mouth, urinary retention, constipation	Tolerability improved by starting with lower doses and uptitrating slowly; consider in patients with sleep disruption, neuropathic pain, mixed migraine and tension type features
Nortriptyline	10–50 mg daily	N/A	Similar to amitriptyline but generally milder	Typically used if amitriptyline is effective but not tolerated
SSRIs:				
Fluoxetine	20–40 mg daily	Level U	Diarrhea, nausea, asthenia, insomnia, rhinitis	May cause or worsen headache in some patients
SNRIs:				
Venlafaxine	37.5–150 mg daily	Level B	Hypertension, sweating, weight loss, nausea, dry mouth, asthenia, insomnia, sexual dysfunction; drug withdrawal syndrome	Most robust evidence among SNRIs; often used for treatment of hot flashes in menopausal women; may cause headache in some patients; unlikely to cause weight gain
Duloxetine	30–120 mg daily	N/A	Nausea	May have a lower side effect burden than venlafaxine; unlikely to cause weight gain
Milnacipran	25–100 mg daily	N/A	Hypertension, hot sweats, constipation, nausea, drug withdrawal syndrome	Clinical impression of higher side effect burden and more significant withdrawal syndrome

TCAs, tricyclic antidepressants; *SSRIs*, selective serotonin reuptake inhibitors; *SNRIs*, serotonin and norepinephrine reuptake inhibitors. AAN/AHS evidence levels: level B: "probably effective for prevention of migraine"; level U: "inadequate or conflicting data to support or refute medication useNB: All antidepressants are off label for preventive treatment of migraine

goal of preventive treatment is to reduce headache frequency, severity, and duration; reduce the need for and improve response to acute treatment; and to reduce migraine-associated disability and improve overall quality of life [5•].

Migraine preventive medications have largely been developed for other indications and later found effective in migraine. Antidepressants, particularly tricyclic antidepressants (TCAs), were among the first medications identified as having preventive benefit for migraine [6]. Two antidepressants, amitriptyline and venlafaxine, have been highly rated in guidelines for preventive treatment of migraine [7, 8]. Studies of migraine preventive use in the USA show that tricyclic antidepressants are the second most commonly prescribed medications for migraine prevention, behind topiramate [9].

This review describes the pharmacology of each antidepressant class as it applies to migraine prevention, summarizes the evidence base for each medication, and describes relevant side effects and clinical considerations. Background evidence for this review was obtained from prior systematic reviews and meta-analyses. To ensure that the reported information is current, a PubMed search for each of the individual TCAs, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other antidepressant names with the term "migraine" was conducted in November 2018.

A list of antidepressants with evidence of efficacy for prevention of migraine can be found in Table 1. No antidepressants are FDA approved for the preventive treatment of migraine.

Nociceptive mechanism of antidepressants

The serotonergic and noradrenergic systems are both involved in regulating neuropathic pain, and likely migraine pain as well [10]. Antidepressants target one or both of these systems and their nociceptive properties may be largely related to these effects. Clinical evidence suggests that norepinephrine plays an important role in antinociception [11••]. A review of antidepressants as treatments for neuropathic pain shows better efficacy for drugs that inhibit both norepinephrine and serotonergic reuptake rather than serotonin reuptake alone [12]. Animal studies have also shown that drugs with SNRI activity reduce pain behaviors [13]. For prevention of migraine, TCAs and SNRIs, both of which increase activity of the serotonergic and noradrenergic systems, are more effective than SSRIs.

Tricyclic antidepressants

Tricyclic antidepressants prevent uptake of serotonin and norepinephrine, but also have anticholinergic and antihistaminergic activity [14]. The degree of monoamine reuptake blockade varies by specific TCA. Amitriptyline, which has the best evidence for efficacy in migraine prevention, has a complex pharmacologic profile. It is a potent serotonin reuptake inhibitor and a moderate norepinephrine reuptake inhibitor. It is also metabolized to nortriptyline, which has a stronger effect on the norepinephrine transporter. Amitriptyline also has action at the alpha1 adrenergic receptor in addition to muscarinic acetylcholine receptors and histamine H1 and H2 receptors. It also blocks sodium, calcium, and potassium channels. Amitriptyline is one of many drugs that has been shown to decrease the likelihood of provoked cortical spreading depression in rats [15]. One other possible mechanism of action of amitriptyline is enhancement of descending inhibitory nociceptive pathways [16].

A 2017 systematic review of randomized controlled trials evaluating efficacy of tricyclic antidepressants for prevention of migraine in adults included 12 trials with a total of 1006 participants [17••]. Nine studies evaluated the efficacy of amitriptyline, with placebo, fluoxetine, or venlafaxine as comparators. There were two studies of clomipramine vs placebo, and one of opipramol vs placebo. The studies of amitriptyline vs placebo found a standard mean difference of –0.85 in favor of amitriptyline. Doses in the included studies ranged from 25 to 150 mg daily, with several studies starting at 50 mg daily. This is a higher starting dose than is commonly used in clinical practice and may explain the increased risk of withdrawal due to adverse events in the TCA trials (RR 1.73, 95% CI 1.00–2.99). All relevant trials of amitriptyline vs placebo initiated treatment at relatively high doses (often 25 mg/day or more). Clinical experience suggests that amitriptyline is better tolerated when started at lower doses, such as 5–10 mg nightly, and increased slowly [18].

Neither trial of clomipramine showed a statistically significant benefit for prevention of migraine. There have been no clinical trials evaluating the efficacy of nortriptyline or doxepin monotherapy vs placebo for prevention of typical migraine. Nortriptyline has been used in trials of combinations of preventives and in treatment of vestibular migraine [19, 20]. Use of nortriptyline as a migraine preventive has also been documented in national insurance databases [21, 22]. Nortriptyline is the main metabolite of amitriptyline but has a lower side effect burden. It may be that use of nortriptyline is driven by better tolerability and evidence that TCAs are relatively equipotent for treatment of neuropathic pain [23]. This assumption has not been formally tested.

Amitriptyline received a level B "probably effective" rating in the 2012 American Academy of Neurology/American Academy of Neurology guideline for preventive treatment of episodic migraine [7]. Amitriptyline did not receive a level A assessment solely due to dropout rates greater than 20% in clinical trials. Clomipramine was assessed as having level B negative evidence "probably ineffective" in the AHS/AAN 2012 guidelines.

TCAs may have a significant side effect burden due to their anticholinergic and antihistaminergic activity. The most common side effects include sedation, weight gain, dry mouth, and constipation. Amitriptyline has a high affinity for the muscarinic cholinergic receptor and therefore has a higher incidence of side effects. In comparison, nortriptyline is less active at both the histamine and muscarinic receptors and therefore has a lower side effect profile. Doxepin has less anticholinergic effect than either amitriptyline or nortriptyline [14].

Selective serotonin reuptake inhibitors

Altered serotonergic function is an important component in migraine pathophysiology [24]. Decreased serotonin levels in migraineurs may lower the threshold at which external and internal stimuli trigger a migraine attack [25]. SSRIs increase serotonin levels at the synaptic cleft. The 5-HT2C receptor may be particularly important in migraine susceptibility [26]. Fluoxetine is also a 5-HT2C antagonist and thus was thought to possibly have unique benefit among SSRIs for prevention of headache. Animal studies suggest that fluoxetine may also have an effect through central opioid receptors as well as serotonergic pathways [27]. Despite this

promising background, trials of SSRIs for prevention of migraine have not been positive.

Among the SSRIs, fluoxetine has been most studied as a preventive treatment for migraine. There have been three randomized controlled trials of fluoxetine or S-fluoxetine as migraine prophylaxis. The phase II RCT study of racemic S-fluoxetine showed a reduction of 0.6 headache days per month in the active group over placebo [28]. An RCT of fluoxetine 20 mg daily vs placebo showed a decrease in pain index scores (headache hours × pain intensity) of 93.7 in the active group vs 36.9 in the placebo group [29]. The placebo group had significantly lower pain index values at baseline, however, indicating that randomization may not have been adequate. One additional RCT of fluoxetine 20 mg every other day for 4 weeks, then daily, included 9 patients per arm and favored the fluoxetine group in initial analysis; reanalysis with more sophisticated statistical techniques found no difference between groups [30, 31]. A study comparing amitriptyline alone to amitriptyline combined with fluoxetine showed no difference in improvement between the two groups [32].

A study of fluoxetine 20–40 mg daily in patients with chronic daily headache or migraine compared to placebo showed improvement in mood symptoms and a slight reduction in headache frequency, but not in pain severity [33]. The improvement in mood appeared before any effect on headache symptoms (month 2 vs 3 of the trial).

Other SSRIs have also been evaluated as migraine preventives in single studies. One trial of sertraline 50–100 mg daily for migraine prophylaxis was negative [34]. A study randomizing patients to either amitriptyline 25 mg daily or fluvoxamine 50 mg daily found similar improvements in measures of headache burden [35]. The two arms were reported as separate before and after studies rather than a head-to-head trial. A comparison of escitalopram 10–20 mg daily and venlafaxine 75–150 mg daily found a larger reduction in headache frequency, duration, intensity, and related disability in the venlafaxine group compared to the escitalopram group [36]. There have been several case reports of paroxetine reducing headache days as well [37, 38].

Studies of fluoxetine have generally either been small or have had significant methodological flaws. Based on the limitations in the evidence base, fluoxetine received a rating of "level U: inadequate or conflicting data to support or refute medication use" in the 2012 AAN/AHS guidelines [7]. Fluvoxamine is also classified as level U. The other SSRIs did not have adequate evidence to receive a rating.

SSRIs have a common side effect profile that includes GI upset including nausea and diarrhea, dry mouth, insomnia or sedation, dry mouth, nervousness or agitation, blurred vision, and sexual dysfunction [39]. Abrupt discontinuation of short acting SSRIs can cause a withdrawal syndrome that includes flu-like symptoms, imbalance, sensory disturbances, hyperarousal and insomnia, and nausea. Fluoxetine has the longest half-life of all SSRIs and as such rarely produces a withdrawal syndrome.

Although some patients clearly see benefit for headache with SSRI use, many cases of headache or migraine worsening with use of SSRIs have also been described [40–44]. The reason for this phenomenon is unclear, but supports the role of serotonin in migraine pathophysiology.

Serotonin and norepinephrine reuptake inhibitors

There has been one placebo controlled randomized trial of venlafaxine for migraine prevention. This study randomized 60 patients with migraine to venlafaxine 75 mg daily, venlafaxine 150 mg daily, or placebo [45]. They found a statistically significant decrease in headache days per month in the venlafaxine 150 mg daily arm (4 days/2 weeks) vs placebo (1 day/2 weeks). A study of 52 people with migraine compared venlafaxine (37.5 mg daily titrated to 150 mg daily) to amitriptyline (10 mg daily titrated to 75 mg daily) [46]. This study found positive benefit in both treatment arms with no statistically significant difference between treatments. As mentioned above, venlafaxine was superior to escitalopram in one study [36]. Venlafaxine has also been studied specifically for prevention of vestibular migraine, with venlafaxine showing better benefit than flunarizine or valproate and equal benefit to propranolol in these open-label studies [47, 48].

A prospective, open-label study evaluated the efficacy of duloxetine 30–120 mg daily in patients with migraine and without depression [49]. In the 22 participants who completed the study, headache days per month was reduced by 3.7. In this study, 22 of 27 participants (81%) reported at least one side effect and two discontinued due to side effects. Duloxetine has particularly been studied in patients with comorbid mood disorders discussed below. Milnacipran was studied in an open-label prospective trial of 38 patients with episodic migraine and 7 with chronic migraine [50]. The dose was titrated from 12.5 mg daily to 50 mg twice daily over the course of a month. The number of headache days decreased by 4.2. In this study, 59% of participants experienced at least one adverse event and nine participants, roughly 1/5, withdrew due to medication-related side effects.

Commonly reported side effects of SNRIs include GI disturbance including nausea and constipation, anorexia, dizziness, dry mouth, heat intolerance, and excessive sweating. Fatigue or insomnia have also been reported, and sexual side effects including delayed orgasm can also be very concerning to patients [51••]. SNRIs can have a prominent withdrawal syndrome similar to that with SSRIs, and this may be prolonged [52]. Venlafaxine may have a higher risk of withdrawal symptoms than other SNRIs.

In clinical practice, headache worsening has been reported with use of SNRIs, similar to the effect seen with SSRIs. It is not clear if there is a higher likelihood of headache worsening with one class of medication vs the other.

Other antidepressants

Two case reports describe successful preventive treatment of migraine with mirtazapine [53, 54]. Mirtazapine has been studied more formally for chronic tension–type headache, but not for migraine [55]. A PubMed search targeting other antidepressants, including newer antidepressant classes such as serotonin modulators, showed no studies for prevention of migraine.

Migraine with comorbid mood disorders

In addition to reducing migraine frequency, antidepressants may have the adjunct benefit of treating comorbid mood disorders. Psychiatric comorbidities are highly prevalent in migraine [56•]. Depression is 2–4 times more common in migraineurs compared to the general population, and about one third of people with migraine have depression. Anxiety disorders are also common. Migraine is associated with a 4–5-fold increase in the risk of general anxiety disorder and 3–10 times the risk of panic disorder [56•].

Several studies have specifically evaluated the efficacy of antidepressants in patients with migraine and comorbid depression. One trial randomized 88 prevention-naive participants with migraine and depression per the Hamilton Depression Rating Scale to either citalopram 20 mg daily or amitriptyline 25–50 mg daily for 16 weeks [57]. This study found equal benefit for mood symptoms across both arms of the study, but amitriptyline was a more effective headache preventive (50% reduction in headache frequency seen in 35/44 amitriptyline vs 17/44 citalopram). An open-label study from the London Migraine Clinic evaluated sertraline 25–100 mg daily + eletriptan 40 mg prn migraine in women with migraine and depression as assessed by the PHQ-9 [58].The authors found a duration-of-treatment-associated reduction in headache days as well as improvement in overall quality of life. A trial compared paroxetine 20 mg BID in 24 patients with migraine and generalized anxiety disorder [59]. In this open-label study, headache frequency reduced by almost 50% in the study population and anxiety scores also decreased. There was no correlation between the reduction in measures of anxiety and reduction in headache days, suggesting independent effects.

Duloxetine 60 mg daily for 8 weeks was tested in 30 patients with major depressive disorder and chronic headache (including migraine and tension-type headache) [60]. Duloxetine treatment in this open-label trial reduced both depression and pain scores in this study. Another study evaluated duloxetine 30–60 mg daily in an open-label study of patients with chronic migraine, medication overuse headache, and major depression [61]. This study further looked at whether the presence of obsessive compulsive disorder (OCD) modified the response to treatment. Among the 50 patients who completed the study, 64% of them had a > 50% reduction in headache frequency. None of the 14 participants with OCD were in the 50% responder group.

Antidepressant co-prescription with triptans

In 2006, the FDA added a black box warning to the co-prescription of SSRI/SNRI antidepressants and triptan antimigraine drugs due to concerns about possible serotonin syndrome [62]. A subsequent review of the cases that informed the FDA decision found that none met modern criteria for serotonin syndrome [63]. A 2010 American Headache Society position paper, citing this evidence, notes that "The currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to concerns for serotonin syndrome." [64]. Despite this, there is ongoing widespread concern among providers, pharmacists, and insurance companies

about the use of this combination due the ongoing black box warning. The most recent evidence supporting safe use of this combination comes from an electronic health record database including information for over 6.5 million patients in a single city. A search of this database found 19,017 patients with co-prescription of an SSRI or SNRI and a triptan [65]. Of the 17 cases of confirmed serotonin syndrome in this population, only 2 used triptans in close proximity to diagnosis, and symptoms had started prior to triptan initiation in both cases. Based on this, the risk of serotonin syndrome with co-prescription of SSRIs/SNRIs and triptans seems extremely low, and antidepressant monotherapy should not be considered a contraindication to triptan use.

Tachyphylaxis

Tachyphylaxis, also known as medication tolerance, is a decline in medication efficacy with continued use in a single patient. Rates of tachyphylaxis to antidepressants used to treat depression can be as high as 50%. [66] This phenomenon in migraine prophylaxis is not well studied. One retrospective study of 176 patients in the 1980s found that 13% of patients reported tachyphylaxis, and that the duration before this effect was seen varied by medication. [67] A more recent review estimated that 1–8% of patients who used migraine preventive treatments developed tolerance to medications. [68] The authors of this review also note that there are multiple possible mechanisms that might lead to tolerance, including pharmacokinetic, pharmacodynamic, behavioral, and cross tolerance. Whether tachyphylaxis is more likely to occur with antidepressants than with other classes of preventive medications is an area for further study.

Use in clinical practice

Antidepressants have an important role in the prevention of migraine. Amitriptyline particularly is one of the most commonly prescribed migraine preventive medications and has strong evidence for efficacy [69]. Amitriptyline is particularly useful in patients who have disordered sleep, in whom the sedating side effect of amitriptyline may improve sleep initiation and maintenance. It can be helpful to instruct patients to take amitriptyline at least an hour before bedtime to ensure that sedation does not linger into the following morning. Amitriptyline may also be useful in patients with comorbid neuropathic or musculoskeletal pain, or in whom there are mixed migrainous and tension-type features [70]. It should be avoided in overweight or obese patients, or in those with glaucoma.

Nortriptyline may be used if patients respond well to amitriptyline but do not tolerate it. Nortriptyline is sometimes initiated instead of amitriptyline if there is concern about the anticholinergic side effects of amitriptyline. This may occur in patients who are elderly or in those with urinary retention or constipation, for example.

Venlafaxine is most commonly used in patients who have failed first line migraine preventive treatments, mostly due to weaker evidence for efficacy. It has the advantage of being weight neutral to weight negative, unlike most other migraine preventive medications [71]. It may also be considered if untreated

comorbid depression is a contributing factor to migraine frequency or migraine-associated disability. Patients should be counseled about the possibility for withdrawal effects. Clinical experience suggests that patients frequently expect medication side effects to resolve with cessation of treatment, and distress related to prolonged withdrawal effects can be significant.

Based on recent studies, the level of evidence assessment for duloxetine for migraine prevention is likely to equal that of venlafaxine in future guidelines. Duloxetine is a reasonable alternative to venlafaxine and may have a lower incidence of withdrawal effects. It is not clear whether a patient who has not responded to venlafaxine might still respond to duloxetine. In clinical practice, this is a common treatment strategy in patients with refractory migraine.

The evidence for efficacy of other antidepressants as migraine preventives is poor. Use of a treatment like fluoxetine might be helpful if depression seems to be the primary factor contributing to poor quality of life in patient presenting with migraine. Treatment of depression is beyond the scope of this article, but patients should be monitored for the possibility of increased suicidality after starting an SSRI/SNRI.

A patient with comorbid depression and migraine may have a discordant response to antidepressant treatment, with improvement in depressive symptoms but not migraine. In this case, it is often helpful to continue the antidepressant while trials of other migraine preventives are ongoing.

Conclusions

Antidepressants are commonly used as migraine preventives. Amitriptyline has the best evidence for use in migraine prevention, but nortriptyline is an alternative tricyclic in patients who may not tolerate amitriptyline. The sedating effect of TCAs can be beneficial for patients with comorbid insomnia. SNRIs including venlafaxine and duloxetine also have evidence for efficacy and may be the most effective treatments in patients with comorbid depression and migraine. SSRIs including fluoxetine are not effective for most patients and are infrequently used. The side effect burden of antidepressants can be substantial. Patients should be particularly counseled about the possibility of a withdrawal effect from SNRIs. There can be significant variation among individuals in sensitivity to the therapeutic and adverse effects from these medications, and the dosing ranges used are therefore wide.

Compliance with Ethical Standards

Conflict of Interest
The author declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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