Using SNRIs to prevent migraines in patients with depression

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For some patients, an antidepressant may be able to treat depression and anxiety, and reduce migraine frequency

Ms. D, age 45, has major depressive disorder (MDD), generalized anxiety disorder (GAD), migraines, and hypertension. At a follow-up visit, she says she has been under a lot of stress at work in the past several months and feels her antidepressant is not working well for her depression or anxiety. Ms. D notes that lately she has had more frequent migraines, occurring approximately 4 times per month during the past 3 months. She describes a severe throbbing frontal pain that occurs primarily on the left side of her head, but sometimes on the right side. Ms. D says she experiences nausea, vomiting, and photophobia during these migraine episodes. The migraines last up to 12 hours, but often resolve with sumatriptan 50 mg as needed.

Ms. D takes fluoxetine 60 mg/d for depression and anxiety, lisinopril 20 mg/d for hypertension, as well as a women's multivitamin and vitamin D3 daily. She has not tried other antidepressants and misses doses of her medications about once every other week. Her blood pressure is 125/80 mm Hg; heart rate is 80 beats per minute; and temperature is 37° C. Ms. D's treatment team is considering switching her to a medication that can act as preventative therapy for migraines while also treating her depression and anxiety.

Migraine is a chronic, disabling neurovascular disorder that affects approximately 15% of the United States population.[1] It is the second-leading disabling condition worldwide and may negatively affect social, family, personal, academic, and occupational domains.[2] Migraine is often characterized by throbbing pain, is frequently unilateral, and may last 24 to 72 hours.[3] It may occur with or without aura and can be associated with nausea, vomiting, or sensitivity to light.[3] Episodic migraines occur <15 days a month, while chronic migraines occur ≥15 days a month.[4]

Many psychiatric, neurologic, vascular, and cardiac comorbidities are more prevalent in individuals who experience

Practice Points

- Evidence suggests that certain serotonin-norepinephrine reuptake inhibitors (SNRIs) **can reduce the frequency of migraines**.
- An SNRI might be an option for a patient **with migraines and comorbid depression or anxiety**.
- Due to its relatively lower incidence of withdrawal symptoms compared to venlafaxine, **duloxetine may be preferred** for patients who have difficulty with medication adherence.
- **Tricyclic antidepressants are also effective** in reducing migraine frequency, but have a higher incidence of adverse effects than SNRIs.

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Table

SNRIs used to prevent migraines

Medication	Dosage range	Common adverse effects	Comments
Venlafaxine	75 to 225 mg/d	Diaphoresis, weight loss (dose-dependent), nausea, xerostomia, dizziness, drowsiness, insomnia, asthenia[9]	Functions as an SSRI at low doses, with increasing norepinephrine reuptake at higher doses[9] When discontinuing, gradually taper over ≥4 weeks to minimize withdrawal symptoms[10] Venlafaxine may have a higher risk of withdrawal symptoms than other SNRIs[8]
Duloxetine	20 to 30 mg twice daily or 60 mg/d; up to 120 mg/d[11,12]	Weight loss, abdominal pain, nausea, vomiting, xerostomia, drowsiness, fatigue[13]	60 to 120 mg recommended for prevention of migraines[12,14] Avoid in patients with liver disease based on relatively greater risk of liver injury compared to other SNRIs Fewer withdrawal effects compared to other SNRIs[8]
Milnacipran	Major depressive disorder: 100 mg/d[15]	Headache, insomnia, hot flash, nausea, constipation[16]	Evidence is scarce regarding the use of milnacipran for migraine prevention Generally not recommended in patients age <18[17]

SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

migraine headaches compared to the general population. Common psychiatric comorbidities found in patients with migraines are depression, bipolar disorder, GAD, panic disorder, and posttraumatic stress disorder[5]; MDD is the most common.[4] A person who experiences migraine headaches is 2 to 4 times more likely to develop MDD than one who does not experience migraine headaches.[4]

First-line treatments for preventing migraine including divalproex, topiramate, metoprolol, propranolol, and timolol.[6] However, for some patients with migraines and comorbid depression or anxiety, an antidepressant may be an option. This article briefly reviews the evidence for using antidepressants that have been studied for their ability to decrease migraine frequency.

Antidepressants that can prevent migraine

Tricyclic antidepressants (TCAs) are second- or third-line options for migraine prevention.[6] While TCAs have proven to be effective for preventing migraines, many patients are unable to tolerate their adverse effects (ie, anticholinergic effects, sedation).[7] TCAs may be more appealing for younger patients, who may be less bothered by anticholinergic burden, or those who have difficulty sleeping.

Serotonin-norepinephrine reuptake inhibitors (SNRIs). There has been growing interest in understanding the potential utility of SNRIs as a preventative treatment for migraines. Research has found that SNRIs are as effective as TCAs for preventing migraines and also more tolerable in terms of adverse effects.[7] SNRIs such as venlafaxine and duloxetine are currently prescribed off-label to prevent migraines despite a lack of FDA approval for this indication.[8]

Understanding the safety and efficacy of SNRIs as preventative treatment for episodic migraines is useful, particularly for patients with comorbid depression. The ***Table***[8-17] details clinical information related to SNRI use.

Duloxetine has demonstrated efficacy in preventing migraines in patients with

Clinical Point

SNRIs are as effective as TCAs for preventing migraines and more tolerable in terms of adverse effects

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Drug Brand Names

Divalproex • Depakote
Duloxetine • Cymbalta
Fluoxetine • Prozac
Lisinopril • Zestril, Prinivil
Milnacipran • Savella
Sumatriptan • Imitrex
Topiramate • Topamax
Venlafaxine • Effexor

Clinical Point

Venlafaxine has demonstrated efficacy for preventing migraines in patients with comorbid depression

comorbid depression.[8] In a 2019 study, Kisler et al[14] found that duloxetine 60 mg/d for 7 weeks was more effective for migraine prophylaxis than placebo as measured by the percentage of self-estimated migraine improvement by each patient compared to pretreatment levels (duloxetine: 52.3% ± 30.4%; placebo: 26.0% ± 27.3%; $P = .001$).

Venlafaxine has also demonstrated efficacy for preventing migraines in patients with comorbid depression.[8] One study demonstrated a significant decrease in headaches per month with the use of venlafaxine 150 mg/d compared to placebo.[18] Adelman et al[19] found a reduction in migraine headaches per month (16.1 to 11.1, $P < .0001$) in patients who took venlafaxine for an average of 6 months with a mean dose of 150 mg/d. In a study of patients who did not have a mood disorder, Tarlaci[20] found that venlafaxine reduced migraine headache independent of its antidepressant action.

Though milnacipran has not been studied as extensively as other SNRIs, evidence suggests it reduces the incidence of headaches and migraines, especially among episodic migraine patients. Although it has an equipotent effect on both serotonin and norepinephrine (NE) reuptake, milnacipran has a greater NE effect compared to other SNRIs approved for treating mood disorders. A prospective, single-arm study by Engel et al[21] found a significant ($P < .005$) reduction from baseline in all headache and migraine days per month with the use of milnacipran 100 mg/d over the course of 3 months. The number of headache days per month was reduced by 4.2 compared to baseline. This same study reported improved functionality and reduced use of acute and symptomatic medications overall due to the decrease in headaches and migraines.[21]

In addition to demonstrating that certain SNRIs can effectively prevent migraine, some evidence suggests certain patients may benefit from the opportunity to decrease pill burden by using a single medication to treat both depression and migraine.[22] Duloxetine may be preferred for patients who struggle with adherence (such as Ms. D) due to its relatively lower incidence of withdrawal symptoms compared to venlafaxine.[8]

CASE CONTINUED

Ms. D's psychiatrist concludes she would be an appropriate candidate for treatment with an SNRI due to her history of MDD and chronic migraines. Because Ms. D expresses some difficulty remembering to take her medications, the psychiatrist recommends duloxetine because it is less likely to produce withdrawal symptoms compared to venlafaxine. To decrease pill burden, fluoxetine 60 mg is stopped with no taper due to its long half-life, and duloxetine is started at 30 mg/d, with a planned increase to 60 mg/d after 1 to 2 weeks as tolerated to target both mood and migraine prophylaxis. Duloxetine will not interact with Ms. D's current medication regimen, including lisinopril, women's multivitamin, or vitamin D3. The psychiatrist discusses the importance of medication adherence to improve her conditions effectively and safely. Ms. D's heart rate and blood pressure will continue to be monitored.

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Clinical Point

Duloxetine has fewer withdrawal effects than other SNRIs, and may be preferred for patients who struggle with adherence