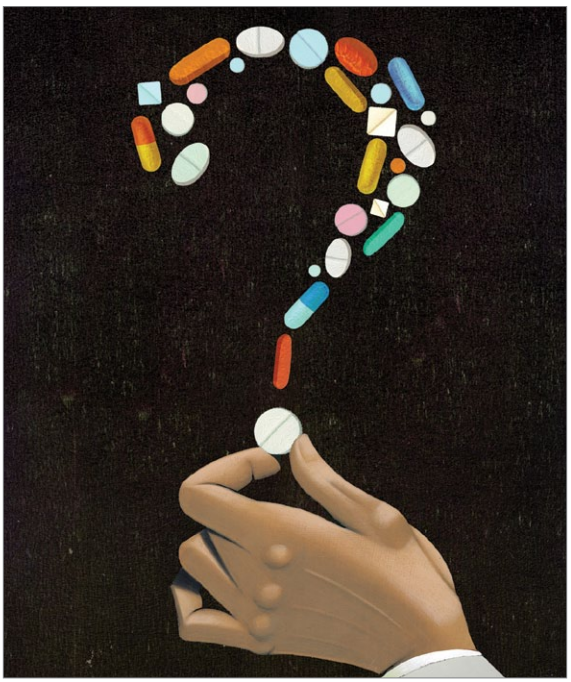
Current PSYCHIATRY
Web extra

Antipsychotics for migraines, cluster headaches, and nausea

Evidence of efficacy for these conditions is limited, and risk of side effects may inhibit use



JON KRAUSE FOR CURRENT PSYCHIATRY

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Most evidence supporting antipsychotics as a treatment for migraine headaches and cluster headaches is based on small studies and chart reviews. Some research suggests antipsychotics may effectively treat nausea but side effects such as akathisia may limit their use.

Migraine headaches

Antipsychotic treatment of migraines is supported by the theory that dopaminergic hyperactivity leads to migraine headaches (***Table 1, page E2***). Antipsychotics have been used off-label in migraine patients who do not tolerate triptans or have status migrainosus—intense, debilitating migraine lasting >72 hours.[1] Primarily a result of D2 receptor blockade, the serotonergic effects of some second-generation antipsychotics (SGAs) may prevent migraine recurrence. The first-generation antipsychotics (FGAs) prochlorperazine, droperidol, haloperidol, and chlorpromazine have been used for migraine headaches (***Table 2, page E3***).[1-27]

Prochlorperazine may be an effective treatment of acute headaches[9] and refractory chronic daily headache.[10] Studies show that buccal prochlorperazine is more effective than oral ergotamine tartrate[11] and IV prochlorperazine is more effective than IV ketorolac[12] or valproate[28] for treating acute headache.

Evidence suggests that chlorpromazine administered IM[2] or IV[3] is better than placebo for managing migraine pain. In a study comparing IV chlorpromazine, lidocaine, and dihydroergotamine, patients treated with chlorpromazine showed more persistent headache relief 12 to 24 hours post-dose.[4] In another study, IV chlorpromazine, 25 mg, was as effective as IM ketorolac, 60 mg.[5]

continued

Clinical Point

Primarily a result of D2 receptor blockade, the serotonergic effects of some SGAs may prevent migraine recurrence

Table 1

Possible rationale for antipsychotic use for headaches and nausea

Condition	Possible rationale
Migraine	Patients are hypersensitive to dopamine agonists or dopamine transporter dysfunction. Some evidence that the dopamine D2 (DRD2) gene is involved
Cluster headache	Pain alleviation possibly related to dopamine receptor antagonism
Nausea	D2 and H1 receptor blockage

Droperidol has been shown to be effective for managing headache, specifically status migrainosus.[6] Patients with "benign headache"—headache not caused by an underlying medical disorder—who received droperidol reported greater reduction in visual analog pain scores within 1 hour of dosing compared with those taking prochlorperazine.[7] In a randomized trial comparing IM droperidol and IM meperidine, patients with an acute migraine who received droperidol had improved scores on the visual pain analog scale and required less "rescue medication" for breakthrough pain.[8] The FDA has issued a "black-box" warning of QTc prolongation with droperidol.

In a double blind, placebo-controlled trial, IV haloperidol, 5 mg, effectively treated migraine headache in 80% of patients compared with 15% of those who received placebo. However, 16% of patients considered the side effects—mainly sedation and akathisia—intolerable and 7% had symptom relapse.[13] In an open-label trial of 6 patients with migraine headache, all patients achieved complete or substantial headache relief 25 to 65 minutes after receiving IV haloperidol, 5 mg.[14]

SGAs often antagonize 5-HT1D receptors and theoretically can render triptan therapy—which stimulates pre-synaptic 5-HT1D receptors—ineffective. This has not been seen clinically and instead, dose-related, non-specific headaches are a common adverse event with SGAs.[29,30] A retrospective chart review found olanzapine provided relief for refractory headaches in patients who had failed ≥4 preventive medications. Olanzapine significantly decreased headache days, from 27.5 ± 4.9 before treatment to 21.1 ± 10.7 after treatment. Olanzapine also improved headache severity (measured on a 0 to 10 scale) from 8.7 ± 1.6 before treatment to 2.2 ± 2.1 after treatment.[16] Researchers found that 2.5 or 5 mg of olanzapine relieved acute migraines for most patients, with repeat dosing as needed up to 20 mg/d. For prophylactic treatment, 5 or 10 mg of olanzapine was used. Olanzapine's antinociceptive effect may be related to its action on α-2 adrenoreceptors and to a lesser extent on involvement of opioid and serotonergic receptors.[17]

In a case series, 3 migraine patients who met criteria for chronic daily headache and migraines but did not have a psychiatric disorder reported significant and sustained headache improvement when treated with risperidone.[19] In a case series of 3 migraine patients with co-occurring psychiatric disorders, aripiprazole decreased migraine frequency and severity.[15] Although limited data support quetiapine's efficacy in treating acute migraines, in an open-label, pilot study, patients taking quetiapine, 25 to 75 mg/d, demonstrated a decrease in mean frequency of migraine days from 10.2 to 6.2 and decreased use of rescue medications from 2.3 to 1.2 days per week.[18]

Cluster headaches

Subcutaneous sumatriptan and inhaled oxygen are first-line treatments for cluster headaches.[31] A single, small study[20] reported that chlorpromazine may prevent cluster headaches, which suggests that D2 receptor blockade may treat such headaches. However, limited supporting evidence relegates its use to a second- or third-line therapy.

In an open-label study (N = 5), olanzapine provided some relief of pain associated with cluster headache within 20 minutes of

Table 2

Antipsychotics for headache and nausea: Strength of the evidence

Condition	Strength of evidence[a]
Migraine	Intermediate: Chlorpromazine,[2-5] droperidol,[6-8] prochlorperazine[1,10-12]
	Weak: Haloperidol[13,14]
	Very weak: Aripiprazole,[15] olanzapine,[16,17] quetiapine,[18] ziprasidone[19]
Cluster headache	Weak: Chlorpromazine[20]
	Very weak: Clozapine,[21] olanzapine[22]
Nausea/vomiting	Intermediate: Droperidol,[23] metoclopramide,[24] prochlorperazine,[25] promethazine[25]
	Weak: Olanzapine[26,27]

[a]Strong: Multiple, well-designed RCTs directly relevant to the recommendation, yielding consistent findings
Intermediate: Some evidence from RCTs that support the recommendation, but the scientific support was not optimal
Weak: Consensus recommendation in the absence of relevant randomized controlled trials and better evidence than case report or series
Very weak: Case reports or case series or preliminary studies

RCTs: randomized controlled trials

administration.[22] In another study, patients with schizophrenia and comorbid cluster headaches improved with olanzapine.[21]

Because evidence is limited to small prospective studies, antipsychotic treatment of cluster headache is not well established.[20-22] However, olanzapine may benefit patients with comorbid cluster headaches and schizophrenia.

Nausea

The signaling pathways that mediate emesis involve 5-HT3, D2, muscarinic, and histamine receptors.[32] Before 5-HT3 antagonists were available, the FGAs metoclopramide, droperidol, prochlorperazine, and promethazine were used to manage acute emesis in emergency departments.[23] A double-blind, placebo-controlled trial found IV droperidol, 1.25 mg, was more effective than metoclopramide, 10 mg, or prochlorperazine, 10 mg, for relieving moderate to severe nausea in adult patients.[23] However, droperidol and prochlorperazine were associated with akathisia. In addition, this trial did not find a clinically significant difference between groups—including placebo—in anxiety, sedation, or need for rescue medications.[23] Use of droperidol to treat nausea decreased after the drug received a "black-box" warning for QT prolongation and torsades de pointes.

Metoclopramide is effective for treating acute migraine and associated nausea[24] and has been used to treat gastroparesis because of its effect on upper GI motility. Phenothiazines have been used to treat nausea and studies have shown prochlorperazine to be more effective than promethazine.[25] Some studies of prochlorperazine have reported a 44% incidence of akathisia, which limits the drug's use in patients who may be sensitive to such effects.[33] Promethazine can cause sedation and risk of tissue necrosis at the injection site.[34]

Among SGAs, olanzapine effectively prevented acute and delayed chemotherapy-induced nausea and vomiting in a proof-of-concept study of patients receiving high and moderate emetogenic therapies.[26,27] National Comprehensive Cancer Network guidelines cite olanzapine as a potential option for treating refractory and breakthrough emesis.[35] In a small study (N = 50), olanzapine showed comparable antinausea effect to aprepitant—a neurokinin 1 receptor antagonist—and effectively prevented chemotherapy-induced nausea and vomiting in highly emetogenic chemotherapy.[36]

Clinical Point

A small study reports that chlorpromazine may prevent cluster headaches, which suggests D2 receptor blockade may treat such headaches

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continued

Headache, nausea, and antipsychotics

Clinical Point

Metoclopramide effectively treats acute migraine and associated nausea and has been used for gastroparesis

Related Resources

- Kelley NE, Tepper DE. Rescue therapy for acute migraine, part 2: neuroleptics, antihistamines, and others. Headache. 2012;52(2):292-306.
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Drug Brand Names

Aprepitant • Emend
Aripiprazole • Abilify
Chlorpromazine • Thorazine
Dihydroergotamine • D.H.E 45
Droperidol • Inapsine
Ergotamine tartrate • Ergostat
Haloperidol • Haldol
Ketorolac • Toradol
Lidocaine • Xylocaine, Lidoderm
Meperidine • Demerol
Metoclopramide • Reglan
Olanzapine • Zyprexa
Prochlorperazine • Compazine
Promethazine • Phenergan
Quetiapine • Seroquel
Risperidone • Risperdal
Sumatriptan • Imitrex
Valproate • Depakote

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