

Review Article

Rescue Therapy for Acute Migraine, Part 2: Neuroleptics, Antihistamines, and Others

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Objectives.—This second portion of a 3-part series examines the relative effectiveness of headache treatment with neuroleptics, antihistamines, serotonin antagonists, valproate, and other drugs (octreotide, lidocaine, nitrous oxide, propofol, and bupivacaine) in the setting of an emergency department, urgent care center, or headache clinic.

Methods.—MEDLINE was searched using the terms “migraine” AND “emergency” AND “therapy” OR “treatment.” Reports were from emergency department and urgent care settings and involved all routes of medication delivery. Reports from headache clinics were only included if medications were delivered by a parenteral route.

Results.—Prochlorperazine, promethazine, and metoclopramide, when used alone, were superior to placebo. Droperidol and prochlorperazine were superior or equal in efficacy to all other treatments, although they also have more side effects (especially akathisia). Metoclopramide was equivalent to prochlorperazine and, when combined with diphenhydramine, was superior in efficacy to triptans and non-steroidal anti-inflammatory drugs. Meperidine was inferior to chlorpromazine and equivalent to the other neuroleptics. The overall percentage of patients with pain relief after taking droperidol and prochlorperazine was equivalent to sumatriptan.

Conclusions.—Prochlorperazine and metoclopramide are the most frequently studied of the anti-migraine medications in the emergent setting, and the effectiveness of each is superior to placebo. Prochlorperazine is superior or equivalent to all other classes of medications in producing migraine pain relief. Dopamine antagonists, in general, appear to be equivalent for migraine pain relief to the migraine-“specific” medications sumatriptan and dihydroergotamine, although there are fewer studies involving the last two. Lack of comparisons to placebo and the frequent use of combination medications in treatment arms complicate the comparison of single agents to one other.

Key words: migraine, emergency, treatment, DHE, triptan, magnesium

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NOTE TO THE READER

In part 1 of this review, results of trials involving triptans, dihydroergotamine, and magnesium as rescue medications for migraine administered in emergency departments, urgent care centers, and headache clinic

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infusion centers were reviewed. Pertinent information concerning migraine pathophysiology and the methodology commonly used for studies of rescue migraine therapy also were included.

This article (part 2) focuses on similar studies involving neuroleptics, antihistamines, serotonin antagonists, valproate, and other assorted medications (octreotide, lidocaine, nitrous oxide, propofol, and bupivacaine). Part 3 will address studies involving opioids, non-steroidal anti-inflammatory drugs, steroids, and post-discharge medications.

Explanation of Methodology.—When drugs from 2 different classes of medications were compared,

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Conflict of Interest: None.

a summary of results appears under both classes (for example, a study comparing a neuroleptic to valproate appears under both neuroleptics and valproate), but the details of the results will only appear once. Where combinations of medications were used, all members of the combination are represented within their own medication class.

“NEUROLEPTICS” (DOPAMINE ANTAGONISTS)

Both serotonin (5-HT₃) and dopamine play a role in the pathogenesis of migraine with and without aura. There is an increased frequency of alleles of the dopamine D2 receptor gene in patients diagnosed with migraine with aura.¹ The neuroleptics include, in part, the phenothiazines (eg, prochlorperazine, chlorpromazine, promethazine, and methotrimeprazine); the butyrophenones (eg, droperidol and haloperidol); and metoclopramide. Neuroleptics act on post-synaptic cells as dopamine antagonists, notably in the limbic system and the basal ganglia. Neuroleptics also have substantial anti-adrenergic, anticholinergic, anti-serotonergic, and antihistaminergic effects. As anti-emetics, they act on the chemoreceptor trigger zone of the reticular formation through D2 receptors, and they affect gastrointestinal motility.¹ They are well absorbed, both parenterally and orally (PO).

The most common side effects of neuroleptics are sedation and drowsiness. They also can cause extrapyramidal effects; dystonia and akathisia are seen most often with parenteral dosing and more commonly with prochlorperazine. Dystonia and akathisia may be prevented by premedicating with an anticholinergic agent (eg, benztropine, diphenhydramine, or trihexyphenidyl). Due to their α -adrenergic antagonist effects, postural hypotension infrequently occurs with the phenothiazines, and neuroleptic malignant syndrome is a rare side effect.¹ QT interval prolongation is also a rare side effect and is most likely to occur with droperidol; it can result in a potentially fatal ventricular arrhythmia. Before giving droperidol, an electrocardiogram (ECG) should be done to ascertain that the QTc interval is less than 450 ms. Potassium and magnesium levels also should be checked.²

Four studies compared prochlorperazine delivered by 3 different routes: 1 rectally (PR), 1 intramuscularly (IM), and 2 intravenously (IV) to placebo, as well as to metoclopramide in 2 studies. Jones et al found that prochlorperazine 25 mg PR outperformed placebo as to pain reduction measured via the 11-point pain scale (11-PPS) (-7.6 vs -4.3 ; $P = .018$); no adverse events were reported.³ Jones et al found the percent of patients headache-free at 1 hour was greater with prochlorperazine 10 mg IV vs placebo/normal saline (NS) IV for treating migraine and tension-type headache (74% vs 13%; $P < .001$).⁴ No extrapyramidal reactions were reported. One patient taking prochlorperazine experienced asymptomatic orthostatic hypotension, and drowsiness was similar across treatments (prochlorperazine 17% vs placebo 7%). Coppola et al compared prochlorperazine 10 mg IV to placebo/NS IV and metoclopramide 10 mg IV.⁵ Headache relief at 30 minutes was greater for prochlorperazine than metoclopramide (82% vs 48%; $P = .03$), but there was no difference between metoclopramide and placebo (48% vs 29%; $P = .14$). Pain reduction (11-PPS) was greatest for prochlorperazine, followed by metoclopramide, and then placebo (-7.6 vs -4.2 vs -1.5 ; no inferential statistics reported). Jones et al found the percent pain reduction at 1 hour favored prochlorperazine 10 mg IM over both placebo/NS IM and metoclopramide 10 mg IM (67% vs 34% vs 16%; $P < .01$); the most common side effect was drowsiness for both prochlorperazine (18%) and metoclopramide (17%).⁶

Five studies compared prochlorperazine 10 mg IV as a single agent to another single agent. Seim et al found prochlorperazine outperformed ketorolac 30 mg IV (pain relief measured using the visual analog scale [VAS]: -71 vs -40 ; $P = .04$).⁷ Ginder et al compared prochlorperazine to magnesium 2 g IV.⁸ At 30 minutes, prochlorperazine provided greater pain reduction (VAS) (-47 vs -24 ; $P < .05$). One patient (5%) reported dysphoria with prochlorperazine, and 4 patients (25%) had burning pain at the IV site with magnesium. Tanen et al showed the superiority of prochlorperazine over valproate 500 mg IV for pain reduction (VAS) at 1 hour (-64.5 vs -9.0 ; $P < .01$); there was no difference in sedation between the groups.⁹ Miller et al compared prochlorperazine to

octreotide 100 μg IV.¹⁰ Pain reduction (VAS) was greater for prochlorperazine (-50.5 vs -33.3 ; $P < .01$), as was headache relief (90% vs 57%, $P < .01$). Headache recurrence at 48-72 hours, however, was not less for prochlorperazine (10% vs 25%; $P = .10$). More patients complained of restlessness with prochlorperazine (35% vs 8%; $P < .01$), but there was less sedation (VAS) than with octreotide (-2.7 vs $+19.7$; $P = .03$). Callan et al compared prochlorperazine to another phenothiazine, promethazine 25 mg IV, for treating patients with undifferentiated primary headache.¹¹ Headache relief was greater for prochlorperazine at 30 minutes (69% vs 39%; $P < .01$), but this advantage was not significant at 60 minutes (91% vs 47%; $P = .13$). Patients taking promethazine reported more drowsiness ($P = .002$). The authors summed up their findings stating that while both prochlorperazine and promethazine were effective in emergency headache treatment, prochlorperazine worked faster in providing relief. This means that at 30 minutes, it showed superiority, but by 60 minutes, this advantage no longer showed a statistical difference.

In the last 3 studies, prochlorperazine in combination with a second agent was compared with either single or combination agents. Saadah compared prochlorperazine 5 mg IV plus dihydroergotamine (DHE) 0.5 mg IV to prochlorperazine 10 mg IV plus DHE 1 mg IV, prochlorperazine 3.5 mg IV plus DHE 1 mg IV, and DHE 1 mg IV alone for the treatment of patients with severe headache who chose IV treatment over IM treatment.¹² The percentages pain-free at 4 hours were 80% for prochlorperazine 5 mg + DHE 0.5 mg, 89% for prochlorperazine 3.5 mg + DHE 1 mg, 95% for prochlorperazine 10 mg + DHE 1 mg and 83% for DHE 1 mg alone. Side effects occurred in 100% for those receiving DHE alone, the most common being chest discomfort (75%), nausea (67%), and sedation (30%). Higher doses of prochlorperazine were associated with a higher frequency of side effects, although all doses yielded fewer side effects than were recorded with DHE alone. Sedation and akathisia were less frequent with the 3.5 mg dose, although nausea was slightly more common. Friedman et al compared prochlorperazine 10 mg IV plus diphenhydramine 25 mg IV to metoclopramide 20 mg IV plus diphenhydramine 25 mg IV.¹³ Twenty

percent of patients had headaches lasting longer than 72 hours. There was no difference between prochlorperazine and metoclopramide in pain freedom (57% vs 41%) or pain relief (87% vs 78%) at 2 hours. Reported rates of akathisia (prochlorperazine 46% vs metoclopramide 32%) and drowsiness (prochlorperazine 15% vs metoclopramide 13%) were similar. Kostic et al found greater efficacy for prochlorperazine 10 mg IV plus diphenhydramine 12.5 mg subcutaneously (SQ) compared with sumatriptan SQ 6 mg (pain reduction VAS: -73 vs -50 ; $P < .05$); 9 of 31 patients taking prochlorperazine/diphenhydramine reported restlessness.¹⁴ Table 1 summarizes the studies involving prochlorperazine.

Iserson first investigated the efficacy of chlorpromazine IV 1 mg/kg (max 100 mg) for headache relief using an uncontrolled design.¹⁵ At 1 hour, 96% of patients treated were pain free, and 92% had sustained headache relief at 24 hours. Eighteen percent had orthostatic hypotension, and 11% were symptomatic. There have been reported 2 placebo-controlled studies involving chlorpromazine. While McEwen et al reported that chlorpromazine 1 mg/kg IM was not superior to placebo/NS IM in terms of headache relief (47.4% vs 23.5%; $P = .18$), the percentage of patients requiring rescue medication was significantly less for patients receiving chlorpromazine (42% vs 82%; $P = .014$); more patients taking chlorpromazine reported drowsiness (79% vs 35%; $P < .05$) and had a systolic blood pressure BP drop of >10 mm Hg (53% vs 20%; $P < .05$).¹⁶ Compared with placebo, Bigal et al found a greater percentage of their patients receiving chlorpromazine 0.1 mg/kg IV to be pain free at 1 hour (66.7% vs 6.7%; $P < .01$ for migraine with aura and 63.2% vs 10%; $P < .01$ for migraine without aura).¹ Postural hypotension and drowsiness occurred more often with chlorpromazine (16.7% vs 1.6%; $P < .05$). Nausea and dyspepsia occurred more often with placebo ($P < .05$).

Three studies compared chlorpromazine to 1 or more single active agents. Lane et al found pain reduction (VAS) was greater for chlorpromazine 0.1 mg/kg IV (up to 3 doses) than for meperidine 0.4 mg/kg IV plus dimenhydrinate 25 mg IV (-70.6 vs -44.5 ; $P < .05$).¹⁷ Bell et al compared chlorpromazine 12.5 mg IV (could repeat up to 37.5 mg) to lidocaine

Table 1.—Studies Comparing Prochlorperazine (PCZ) to Other Agents for Migraine Therapy

Study First Author (year)	G1 Treatment	mg or mg/kg	Route	G2 Treatment	mg or mg/kg	Route	Venue – # If Multiple Sites	Research Design	% Women	Mean Age	G1 # pts	G2 # pts	% Pain-Free		% Pain Relief		% Sustained Pain Relief		% Disability Free		% Requiring Rescue		% Patient Satisfaction	
													G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2
Jones et al (1994) ³	PCZ	25	PR	PCB	ND	PR	ED	R/DB/P	95	30	10	10	ND	ND	100	50	ND	ND	ND	ND	30	60	ND	ND
Coppola et al (1995) ⁵	PCZ	10	IV	PCB	ND	IV	ED	R/DB/P	ND	ND	22	24	ND	ND	82	29	ND	ND	ND	ND	9	64	ND	ND
Jones et al (1989) ⁴	PCZ	10	IV	PCB	ND	IV	ED3	R/DB/P	67	32	42	40	74	13	88	45	ND	ND	ND	ND	21	80	ND	ND
Jones et al (1996) ⁶	PCZ	10	IM	PCB	ND	IM	ED	R/DB/P	73	32	28	29	32	7	67	16	ND	ND	ND	ND	57	86	ND	ND
Seim et al (1998) ⁷	PCZ	10	IV	KET	30	IV	ED	R/DB/ND	92	33	29	35	ND	ND	75	52	ND	ND	ND	ND	14	17	ND	ND
Kostic et al (2010) ¹⁴	PCZ	10	IV	STP	6	SQ	ED	R/DB/ND	64	29	31	35	96	70	ND	ND	57	37	ND	ND	ND	ND	ND	ND
plus Ginder et al (2002) ⁸	DPH PCZ	12.5 10	IV IV	MAG	2000	IV	ED	R/DB/ND	69	ND	20	16	40	12	90	56	ND	ND	ND	ND	50	50	ND	ND
Callan et al (2008) ¹¹	PCZ	10	IV	PMZ	25	IV	ED	R/DB/ND	81	29	35	35	ND	ND	69	39	ND	ND	ND	ND	34	34	54	54
Friedman et al (2008) ¹³	PCZ	10	IV	MTC	20	IV	ED	R/DB/ND	90	36	39	38	57	41	87	78	65	47	47	36	9	17	77	73
plus Tanen et al (2003) ⁹	DPH PCZ	25 10	IV IV	DPH VPT	25 500	IV IV	ED	R/DB/ND	64	31	20	19	ND	ND	86	13	ND	ND	ND	ND	25	79	ND	ND
Miller et al (2007) ¹⁰	PCZ	10	IV	OCT	100 µ	IV	ED	R/DB/ND	75	30	20	24	ND	ND	90	57	90	75	ND	ND	10	46	ND	ND
Miner et al (2001) ⁷	PCZ	10	IV	DPD	2.5	IV	ED	R/SB/ND	52	33	86	82	ND	ND	69	90	ND	ND	ND	ND	ND	ND	ND	ND
or Saadah et al (1992) ¹²	PCZ DHE	10 1	IM IV IV	DPD DHE ND	5 1 ND	IM IV ND	CL ND	ND/ND/ND	80	41	28	10	95	83	ND	ND	86	60	ND	ND	ND	ND	ND	ND
plus	DHE	1	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Superior performance is indicated by boldface; if treatment 1 superior, it is also underlined; if treatment 2 superior, it is also italicized. CL = clinic; DB = double blind; DHE = dihydroergotamine; DPD = droperidol; DPH = diphenhydramine; ED = emergency department; G1 = group 1; G2 = group 2; IM = intramuscular; IV = intravenous; KET = ketorolac; MAG = magnesium; MTC = metoclopramide; OCT = octreotide; P = placebo-controlled; PCB = placebo; PMZ = promethazine; PR = per rectum; R = randomized; SB = single blind; SQ = subcutaneous; STP = sumatriptan; VPT = valproate; ND = no data reported.

50 mg IV (could repeat up to 150 mg) and to DHE 1 mg IV (could repeat once).¹⁸ Pain reduction (11-PPS) was greater with chlorpromazine than with either lidocaine or DHE (chlorpromazine -79.5% vs lidocaine -50% vs DHE -36.7% ; $P < .05$). Kelly et al compared chlorpromazine 12.5 mg IV (could repeat up to 37.5 mg) to sumatriptan SQ 6 mg.¹⁹ All patients received IV metoclopramide 10 mg. At 2 hours, there was no difference in pain reduction (VAS) (sumatriptan -63.3 mm vs chlorpromazine -54.3 mm). There were no dystonic reactions reported.

There were no investigations of the efficacy of promethazine as a single agent; promethazine was studied prospectively only in combination with meperidine. Harden et al compared promethazine 25 mg IM plus meperidine 50 mg IM to ketorolac 60 mg IM or to placebo/NS IM; pain relief at 1 hour was similar across treatments (promethazine/meperidine 60% vs ketorolac 44.4% vs placebo 54.5%).²⁰ Davis et al compared promethazine 25 mg IM plus meperidine 75 mg IM to ketorolac 60 mg IM and found no differences in percent pain-free at 30 minutes, 60 minutes, and 6 hours.²¹ Scherl and Wilson also found no significant difference when comparing promethazine 25 mg IM plus meperidine 75 mg IM to DHE 0.5 mg IV plus metoclopramide 10 mg IV; there was more lethargy and dizziness reported with promethazine/meperidine (7.2% vs 3.9%, $P = .006$).²²

Stiell et al compared methotrimeprazine (not available in the USA) 37.5 mg IM to meperidine 75 mg IV plus dimenhydrinate 50 mg IM.²³ There was no significant difference in pain reduction (VAS) for methotrimeprazine vs meperidine/dimenhydrinate (-40.3 vs -46.6 , $P = .27$). There were more reports of prolonged drowsiness with methotrimeprazine (51.7% vs 16.7%; $P = .01$). Table 2 summarizes the studies involving chlorpromazine, promethazine, and methotrimeprazine.

Butyrophenones, neuroleptics acting as potent dopamine receptor antagonists with some antihistamine and anti-serotonergic activity, can rapidly decrease brainstem activity. They are used as antiemetics, sedatives, and antipsychotic agents. As with all neuroleptics, the side effects of butyrophenones include akathisia, dystonia, hypotension, dizziness, drowsiness, and drug-induced parkinsonism.

Butyrophenones can cause QTc prolongation to a degree where there is increased risk of ventricular arrhythmias and cardiac arrest. There have been 9 cases of torsade de pointes reported in 30 years, and all have been with droperidol at doses of 5 mg IV or greater.^{24,25} As noted previously, the likelihood of dystonia or drug-induced parkinsonism with butyrophenones can be lessened by using concomitant anticholinergic medication. Orthostatic hypotension can be avoided by pretreating with a 500 mL NS bolus.

Silberstein et al compared 4 doses of droperidol IM (0.1, 2.75, 5.5, and 8.25 mg) to placebo/NS IM.²⁶ The percentages of subjects pain-free at 2 hours for placebo and droperidol doses 0.1, 2.75, 5.5, and 8.25 mg were 16, 27, 49, 37, and 34%, respectively ($P < .01$). Thirty percent of those receiving 2.75 mg or more of droperidol reported serious side effects, including anxiety, akathisia, and somnolence. No patient had ECG changes showing QT prolongation. Miner et al compared droperidol 5 mg IM or 2.5 mg IV to prochlorperazine 10 mg IM or 10 mg IV.²⁷ There was no difference in efficacy between IM and IV routes for either medication. Pain reduction (VAS) at 1 hour was greater for droperidol (-81.4% vs -66.9% ; $P < .001$). Frequency of side effects for droperidol and prochlorperazine were similar (15.2% vs 9.6%; $P = .19$), with sedation being more common with droperidol (9% vs 1%). Weaver et al also compared droperidol 2.5 mg IV to prochlorperazine 10 mg IV.²⁸ The percentage pain-free at 30 minutes favored droperidol (54.2% vs 37.5%; $P < .01$), but pain reduction (VAS) was not greater for droperidol (-79.1 vs -72.1 ; $P = .23$). The rate of akathisia was similar for both treatments (6% vs 8%; $P = .25$). Richman et al found droperidol 2.5 mg IM and meperidine 1.5 mg/kg IM produced similar pain reduction (VAS) (-47 vs -37 ; $P = .33$); akathisia was reported in 13.3% taking droperidol, with sedation in 6.7% taking droperidol, and 14.3% taking meperidine.²⁹ Hill et al reported that droperidol 5 mg IM was similar to olanzapine 10 mg in the percentage of patients pain-free at 1 hour (droperidol 26% vs olanzapine 38%; $P = .65$).³⁰ Honkaniemi et al compared haloperidol 5 mg in 500 mL NS IV to placebo/NS (500 mL) IV.³¹ Pain reduction (VAS) was greater with haloperidol (-55 vs -9 ; $P < .001$), with 80% of those

Table 2.—Studies Comparing Chlorpromazine (CPZ), Promethazine (PMZ), Methotrimeprazine (MTM), Droperidol (DPD), and Haloperidol (HLP) Individually to Other Agents for Migraine Therapy

Study First Author (year)	G1 Treatment mg/kg	Route	G2 Treatment mg/kg	Route	mg or mg/kg	Venue - # If Multiple Sites	Research Design	% Women	Mean Age	G1 # pts	G2 # pts	% Pain-Free		% Sustained Pain Relief		% Disability-Free		% Requiring Rescue		% Patient Satisfaction		
												G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1
Bigal et al (2002) ¹	CPZ 0.1	IV	PCB	ND	IV	ED2	R/DB/P	71	31	38	30	63	10	ND	ND	ND	ND	ND	8	50	ND	ND
McEwen et al (1987) ¹⁶	CPZ 1	IM	PCB	ND	IM	ED2	R/DB/P with aura	ND	ND	30	30	67	7	ND	ND	ND	ND	ND	8	42	ND	ND
Iserson (1983) ¹⁵	CPZ 1	IM	ND	ND	ND	ED	ND/ND/ND	72	ND	100	ND	96	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Kelly et al (1997) ¹⁹	CPZ 12.5	IV	STP	6	SQ	ED2	R/ND/ND	67	34	23	20	41	42	72	85	ND	ND	ND	ND	ND	ND	95
Lane et al (1989) ¹⁷	CPZ 0.1	IV	MEP	0.4	IV	ED	R/DB/ND	85	31	24	22	ND	ND	ND	ND	ND	ND	ND	8	50	ND	ND
plus Bell et al (1990) ¹⁹	ND	ND	DMH	25	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
also vs Scherl and Wilson (1995) ²²	CPZ 12.5	IV	LDC	50	IV	ED2	R/SB/ND	79	ND	24	26	33	8	80	50	89	29	ND	ND	ND	ND	67
plus Davis et al (1995) ²¹	ND	ND	DHE	1	IV	ND	ND	ND	ND	ND	26	ND	23	ND	ND	37	ND	ND	ND	ND	ND	26
plus Harden et al (1996) ²⁰	PMZ 25	IM	DHE	0.5	IV	ED	R/ND/ND	70	31	13	14	ND	ND	77	86	33	54	ND	ND	ND	ND	ND
also vs Strell et al (1991) ²³	MEP 75	IM	MTC	10	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
plus Richman et al (2003) ²⁶	PMZ 25	IM	KET	60	IM	ED	R/DB/ND	81	35	22	20	21	22	64	50	55	50	ND	ND	ND	ND	ND
also vs Miner et al (2001) ²⁷	MEP 75	IM	ND	ND	ND	ND	ND	ND	ND	ND	10	ND	ND	60	44	ND	ND	ND	ND	ND	ND	ND
plus Hill et al (2008) ³⁰	MEP 50	IM	PCB	ND	IM	ND	ND	ND	ND	ND	10	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
also vs Honkaniemi et al (2006) ³¹	MTM 37.5	IM	MEP	75	IM	ED	R/DB/ND	76	32	37	37	ND	ND	51	59	82	77	ND	ND	ND	30	27
plus Weaver et al (2004) ²⁸	ND	ND	DMH	50	IM	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
also vs Hill et al (2008) ³⁰	DPD 5.5	IM	PCB	ND	IM	CL	R/DB/P	81	41	124	181	40	22	84	61	68	54	ND	ND	ND	21	44
plus Weaver et al (2004) ²⁸	DPD 2.5	IM	MEP	1.5	IM	ED	R/DB/ND	73	32	15	14	ND	ND	53	49	ND	ND	ND	ND	ND	33	43
also vs Hill et al (2008) ³⁰	DPD 2.5	IV	PCZ	10	IV	ED	R/DB/ND	86	31	48	48	54	38	83	72	ND	ND	ND	ND	ND	ND	ND
plus Hill et al (2008) ³⁰	DPD 2.5	IV	PCZ	10	IV	ED	R/SB/ND	52	33	82	86	ND	ND	90	69	ND	ND	ND	ND	ND	ND	ND
also vs Hill et al (2008) ³⁰	DPD 5	IM	PCZ	10	IM	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
plus Honkaniemi et al (2006) ³¹	DPD 5	IM	OLZ	10	IM	ED	R/ND/ND	76	34	42	45	26	38	88	86	ND	ND	ND	ND	ND	ND	ND
also vs Honkaniemi et al (2006) ³¹	HLP 5	IV	PCB	ND	IV	UC	R/DB/P	ND	ND	20	20	ND	ND	80	15	ND	ND	ND	ND	ND	ND	84

Superior performance is indicated by boldface; if treatment 1 superior, it is also underlined; if treatment 2 superior, it is also italicized. CL = clinic; DB = double blind; DHE = dihydroergotamine; DMH = dimenhydrinate; ED = emergency department; G1 = group 1; G2 = group 2; IM = intramuscular; IV = intravenous; KET = ketorolac; LDC = lidocaine; MEP = meperidine; MTC = metoclopramide; P = placebo-controlled; PCB = placebo; PCZ = prochlorperazine; R = randomized; SB = single blind; SQ = subcutaneous; STP = sumatriptan; ND = no data reported.

receiving haloperidol reporting headache relief vs 15% of those given placebo ($P < .001$). Side effects of haloperidol included sedation (53%) and akathisia (53%), with 16% unwilling to take haloperidol again (chiefly because of side effects). Table 2 shows the details of the studies on the butyrophenones.

Metoclopramide is a neuroleptic/anti-emetic that is known to relieve gastroparesis and facilitate analgesic absorption.³² Common side effects include fluid retention (use with caution in patients with congestive heart failure and liver disease), lowered seizure threshold, hypertension, mild sedation, and extrapyramidal effects.

Six studies compared metoclopramide 10 mg IV, 10 mg IM, or 20 mg PR as a single agent to placebo. Three studies showed metoclopramide to be superior to placebo. Tek et al found greater headache relief at 1 hour with metoclopramide 10 mg IV vs placebo/NS IV (67% vs 19%; $P = .02$); 8% of those receiving metoclopramide complained of restlessness.³³ Ellis et al found pain reduction (VAS) was similar for metoclopramide 10 mg IV and metoclopramide plus ibuprofen 600 mg given PO (-75 vs -50) but was greater for both treatments compared with ibuprofen alone or placebo (both -25; $P < .01$).³⁴ Cete et al compared metoclopramide 10 mg IV to magnesium 2 g IV and to placebo/NS IV.³⁵ Pain reduction (VAS) was similar for metoclopramide and magnesium vs placebo (-38 vs -33 vs -24), but a smaller percentage of those receiving metoclopramide and magnesium required rescue medications (38% and 44% vs 65% for placebo; $P = .04$). Three percent of those receiving metoclopramide complained of dystonia, and 8% of those who received magnesium complained of flushing.

Three studies failed to show any superiority of metoclopramide over placebo. Coppola et al reported that metoclopramide 10 mg IV was similar to placebo/NS IV (48% vs 29%; $P = .14$) and inferior to prochlorperazine 10 mg IV (48% vs 82%; $P = .03$).⁵ Jones et al found that metoclopramide 10 mg IM did not decrease migraine pain (VAS) as effectively as prochlorperazine 10 mg IM when both active therapies were compared with placebo/NS IM (metoclopramide 34% vs prochlorperazine 67% vs placebo 16%, $P < .01$).⁶ Tfelt-Hansen et al compared metoclo-

pramide 10 mg IM or 20 mg PR to placebo/NS IM or PR.³⁶ All patients received acetaminophen 1 g PO and diazepam 5 mg PO. Metoclopramide relieved nausea in 86% (compared with 71% for placebo; $P = .04$) but failed to have a significant advantage over placebo in pain relief (48.5% vs 35.3%; $P = .06$).

Friedman et al found metoclopramide 20 mg IV plus diphenhydramine 25 mg IV (dosed up to 4 times) to be superior to sumatriptan 6 mg SQ in the percentage pain-free at 2 hours (59% vs 35%, $P = .04$).³⁷ Friedman et al found metoclopramide 20 mg IV plus diphenhydramine 25 mg IV was similar to prochlorperazine 10 mg IV plus diphenhydramine 25 mg IV.¹³ Haugh et al conducted a small study ($N = 16$) comparing metoclopramide 10 mg IM plus DHE 1 mg IM to DHE alone for the treatment of mild to severe headache; the percent of patients' pain relief was the same in both groups at 1 hour (37.5%).³⁸

In 5 studies, metoclopramide plus DHE was compared with other agents. Klapper and Stanton found a greater percentage of those receiving metoclopramide 5 mg IV plus DHE 1 mg IV had headache relief (4-PPS) at 1 hour compared with ketorolac 60 mg IM (78% vs 33%; $P = .031$).³⁹ In an open-label study, Edwards et al compared metoclopramide 10 mg IV plus DHE 1 mg IV to valproate 500 mg IV; headache relief at 4 hours was the same in both groups (60%).⁴⁰ Belgrade et al compared metoclopramide 10 mg IV plus DHE 1 mg IV to meperidine 75 mg IM plus hydroxyzine 50 mg IM and to butorphanol 2 mg IM; pain reduction (VAS) was significantly greater for DHE plus metoclopramide (-59) and butorphanol (-54) vs meperidine/hydroxyzine (-37; $P < .01$).⁴¹ Klapper and Stanton found pain reduction (4-PPS) was greater for metoclopramide 10 mg IV plus DHE 1 mg IV than meperidine 75 mg IV plus hydroxyzine 75 mg IM (-2.14 vs -0.86; $P = .006$).⁴² Scherl and Wilson found no difference between metoclopramide 10 mg IV plus DHE 0.5 mg IV and meperidine 75 mg IV plus promethazine 25 mg IM.²²

Friedman et al compared 3 doses of IV metoclopramide (10, 20, and 40 mg).⁴³ Pain reduction (11-PPS) at 1 hour was similar across doses (-4.7 vs -4.9 vs -5.3; $P = .19$). Sustained pain freedom for all

doses was low (16% vs 20% vs 21%). The rate of drowsiness at 1 hour was 69%. At 48 hours' follow up, patients reported severe drowsiness (17%), akathisia (9%), and dizziness (8%) with similar rates across doses. Table 3 summarizes the studies involving metoclopramide.

OTHER ANTI-EMETICS; ANTIHISTAMINES AND 5HT₃ ANTAGONISTS

Chiefly for their anti-emetic and sedative properties, the antihistamines diphenhydramine, dimenhydrinate, and hydroxyzine are usually combined with another agent when used for acute migraine. Diphenhydramine also is used to prevent akathisia and dystonic reactions. Based on clinical experience, it is widely held that these agents also can boost the headache-relieving properties of analgesics, perhaps through preventing further mast cell degranulation (which can contribute to peripheral inflammation). A small number of studies have treatment arms containing these antihistamines, although only 1 study compares an antihistamine, hydroxyzine, as a single agent to placebo.

Friedman et al compared diphenhydramine 25 mg IV plus metoclopramide 20 mg IV (up to 4 doses) to sumatriptan 6 mg SQ.³⁷ Pain reduction (11-PPS) was not different between groups at 2 hours (sumatriptan -6.3 vs metoclopramide plus diphenhydramine -7.2) or at 24 hours (sumatriptan -5.0 vs metoclopramide plus diphenhydramine -6.1). Common side effects included weakness, drowsiness, and a feeling of heaviness, with only the last being seen more with sumatriptan (11% vs 0%; $P = .05$).

Friedman et al compared diphenhydramine 25 mg IV plus trimethobenzamide 200 mg IM to sumatriptan 6 mg SQ.¹³ The study originally was designed only to demonstrate that the combination of trimethobenzamide and diphenhydramine was superior to sumatriptan, which the investigators failed to demonstrate. Pain reduction (11-PPS) at 2 hours was similar (trimethobenzamide/diphenhydramine -4.4 vs sumatriptan -6.1). Kostic et al compared diphenhydramine 12.5 mg IV plus prochlorperazine 10 mg IV to sumatriptan 6 mg SQ.¹⁴ Pain reduction (VAS) was significantly greater

for the diphenhydramine/prochlorperazine group (-73 vs -50; $P < .05$). Nine of 31 patients in the prochlorperazine/diphenhydramine group reported restlessness, but none needed treatment. Lane et al found that the combination of dimenhydrinate 25 mg IV plus meperidine 0.4 mg/kg IV was not as effective as chlorpromazine 0.1 mg/kg IV (up to 3 doses).¹⁷ Stiell et al found no advantage of dimenhydrinate 50 mg IV plus meperidine 75 mg IM over methotrimprazine 37.5 mg IM.²³

Tek and Mellon compared hydroxyzine 50 mg IM, nalbuphine 10 mg IM, a combination of hydroxyzine and nalbuphine IM, and placebo/NS IM; for patients without aura, headache relief at 1 hour was greatest in the nalbuphine alone group compared with the other groups (nalbuphine -2.16 vs nalbuphine/hydroxyzine -1.42 vs hydroxyzine -1.00 vs placebo -0.89; $P < .01$).⁴⁶ Belgrade et al compared hydroxyzine 50 mg IM plus meperidine 75 mg IM to DHE 1 mg IV plus metoclopramide 10 mg IV and to butorphanol 2 mg IM; pain reduction (VAS) was significantly greater with DHE/metoclopramide (-59) and butorphanol (-54) vs meperidine/hydroxyzine (-37; $P < .01$).⁴¹ Duarte et al found pain reduction (VAS) with hydroxyzine 50 mg IM plus meperidine 100 mg IM was similar to ketorolac 60 mg IM (-33.7 vs -33.5; $P = .76$); nausea and drowsiness were not more frequent with hydroxyzine/meperidine (48% vs 28%; $P = .15$).⁴⁷ Klapper and Stanton compared hydroxyzine 75 mg IV plus meperidine 75 mg IM to DHE 1 mg IV plus metoclopramide 10 mg IV; pain reduction (4-PPS) was greater with DHE/metoclopramide (-2.14 vs -0.86; $P = .006$).⁴²

Granisetron, a 5-HT₃ antagonist, is useful as an anti-emetic in the treatment of migraine. Other 5-HT₃ receptor antagonists have been shown to reduce inflammatory pain in rats.⁴⁸ Rowat et al compared granisetron 40 and 80 μ g IV to placebo/NS IV.⁴⁹ Neither dose of granisetron produced greater pain reduction (VAS) at 2 hours compared with placebo (40 μ g -15 vs 80 μ g -13 vs placebo -10). Side effects included gastrointestinal GI symptoms, dizziness, and altered taste. Table 4 summarizes the studies involving the antihistamines and 5HT₃ antagonists.

Table 3.—Studies Comparing Metoclopramide (MTC) to Other Agents for Migraine Therapy

Study First Author (Year)	G1 Treatment	mg or mg/kg	Route	G2 Treatment	mg or mg/kg	Route	Venue - # If Multiple Sites	Research Design	% Women	Mean Age	G1 # pts	G2 # pts	% Pain-Free		% Sustained Pain Relief		% Disability-Free		% Requiring Rescue		% Patient Satisfaction			
													G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2
Coppola et al (1995) ⁵	MTC	10	IV	PCB	ND	IV	ED	R/DB/P	ND	ND	24	24	ND	ND	48	29	ND	ND	ND	ND	25	64	ND	ND
Tek et al (1990) ³³	MTC	10	IV	PCB	ND	IV	ED	R/DB/P	ND	ND	25	25	ND	ND	67	19	ND	ND	ND	ND	33	81	ND	ND
Cete et al (2004) ³⁵	MTC	10	IV	PCB	ND	IV	ED	R/DB/P	84	40	37	40	ND	ND	52	35	57	48	ND	ND	38	65	ND	ND
Ellis et al (1993) ³⁴	MTC	10	IV	PCB	ND	IV	ED	R/DB/P	ND	ND	10	10	ND	ND	88	31	ND	ND	ND	ND	ND	ND	ND	ND
Cicek et al (2004) ⁴⁴	MTC	10	IV	PCB	ND	IV	ED	R/DB/P	88	39	50	48	ND	ND	85	56	ND	ND	ND	ND	14	57	ND	ND
Jones et al (1996) ⁶	MTC	10	IM	PCB	ND	IM	ED	R/DB/P	73	32	29	29	14	7	34	16	ND	ND	ND	ND	79	86	ND	ND
Treit-Hansen et al (1980) ³⁶	MTC	20	IM	PCB	ND	IM	CL	R/DB/P	89	41	99	51	ND	ND	48	35	ND	ND	ND	ND	ND	ND	ND	ND
Friedman et al (2008) ¹³	MTC	20	IV	PCZ	10	IV	ED2	R/DB/ND	90	36	38	39	41	57	78	87	47	65	36	47	17	9	73	77
Haugh et al (1992) ³⁸	MTC	10	IV	DHE	1	IV	CL	R/DB/ND	94	36	8	8	25	13	38	38	87	86	87	57	ND	ND	ND	ND
plus Edwards et al (2001) ⁴⁰	DHE	1	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
plus Belgrade et al (1989) ⁴¹	MTC	10	IV	MEP	75	IM	ED	R/ND/ND	63	30	21	22	ND	ND	38	0	>90 pain reduction	ND	ND	ND	ND	ND	ND	ND
plus Klapper and Stanton (1993) ⁴²	DHE	1	IV	HDX	50	IM	ND	R/DB/ND	ND	ND	14	14	ND	ND	93	21	ND	ND	ND	ND	ND	ND	ND	ND
plus Scherl and Wilson (1995) ²²	MTC	10	IV	MEP	75	IM	ED	R/ND/ND	70	31	14	13	ND	ND	86	77	54	33	ND	ND	ND	ND	ND	ND
plus Klapper and Stanton (1991) ³⁹	DHE	0.5	IV	PMZ	25	IM	ND	ND	ND	ND	9	9	ND	ND	78	33	100	89	ND	ND	ND	ND	ND	ND
plus Friedman et al (2005) ³⁷	MTC	5	IV	KET	60	IM	CL	R/DB/ND	ND	ND	9	9	ND	ND	78	33	100	89	ND	ND	11	67	ND	ND
plus Friedman et al (2011) ⁴³	DHE	1	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	MTC	20	IV	STP	6	SQ	ED2	R/DB/ND	80	34	40	38	59	35	83	79	40	27	ND	ND	5	26	87	73
plus Friedman et al (2011) ⁴³	DPH	25	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	MTC	10	IV	MTC	40	IV	ED	R/DB/ND	78	38	113	118	43	44	82	86	16	20	63	69	20	18	74	77

Superior performance is indicated by boldface; if treatment 1 superior, it is also underlined; if treatment 2 superior, it is also italicized. CL = clinic; DB = double blind; DHE = dihydroergotamine; DPH = diphenhydramine; ED = emergency department; G1 = group 1; G2 = group 2; HDX = hydroxyzine; IM = intramuscular; IV = intravenous; KET = ketorolac; MEP = meperidine; P = placebo-controlled; PCB = placebo; PCZ = prochlorperazine; PMZ = promethazine; R = randomized; SQ = subcutaneous; STP = sumatriptan; VPT = valproate; ND = no data reported.

Table 4.—Studies Comparing Diphenhydramine (DPH), Trimethobenzamide (TMB), Hydroxyzine (HDX), Granisetron (GNT), Valproate (VPT), Nitrous Oxide (NOX), Propofol (PPF), Octreotide (OCT), and Lidocaine (LDC) Individually to Other Agents for Migraine Therapy

Study First Author (year)	G1 Treatment mg/kg	Route	G2 Treatment mg/kg	Route	Venue – # If Multiple Sites	Research Design	% Women	Mean Age	G1 # pts	G2 # pts	% Pain-Free		% Sustained Pain Relief		% Disability-Free		% Requiring Rescue		% Patient Satisfaction		
											G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1
Kostic et al (2010) ¹⁴	DPH 12.5	IV	STP 6	SQ	ED	R/DB/ND	64	29	31	35	ND	ND	57	37	ND	ND	ND	ND	ND	ND	
plus Friedland et al (2006) ⁴⁵	PCZ 10	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
Friedman et al (2005) ³⁷	DPH 25	IV	STP 6	SQ	ED	R/DB/ND	92	33	20	20	30	45	70	80	85	75	84	53	20	30	70
plus Friedman et al (2005) ³⁷	TMB 200	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
plus Stiell et al (1991) ²⁵	DMH 50	IM	MTM 37.5	IM	ED	R/DB/ND	76	32	37	37	ND	ND	ND	ND	82	ND	ND	ND	27	30	ND
plus Lane et al (1989) ¹⁷	MEP 75	IM	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
plus Tek and Mellon (1987) ⁴⁶	DMH 25	IV	CPZ 0.1/	IV	ED	R/DB/ND	85	31	22	24	ND	ND	56	85	ND	ND	ND	ND	50	8	ND
plus Edwards et al (2001) ⁴⁰	MEP 0.4/	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
plus Duarte et al (1992) ⁴⁷	HDX 50	IM	PCB	IM	ED	R/DB/P	75	29	19	18	ND	ND	25	23	ND	ND	ND	ND	ND	ND	ND
plus Rowat et al (1991) ⁴⁹	ND	ND	ND	ND	ND	with aura	ND	ND	5	6	ND	ND	50	13	ND	ND	ND	ND	ND	ND	ND
plus Mathew et al (2000) ³¹	HDX 50	IM	KET 60	IM	ED	R/DB/ND	80	35	25	25	ND	ND	20	24	ND	ND	ND	ND	ND	ND	ND
plus Trainer et al (1999) ⁵²	MEP 100	IM	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
plus Krusz et al (2000) ⁵³	GNT 0.08	IV	PCB	IV	ED	R/DB/P	71	40	10	8	ND	ND	22	14	ND	ND	ND	ND	65	75	ND
plus Miller et al (2007) ¹⁰	VPT 500	IV	MTC 10	IV	ED	R/ND/ND	88	42	20	20	ND	ND	50	45	60	90	ND	ND	ND	ND	ND
plus Bell et al (1990) ¹⁸	ND	ND	DHE 1	IV	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
plus Tanen et al (2003) ⁹	VPT 500	IV	CPZ 10	IV	ED	R/DB/ND	64	31	19	20	ND	ND	13	86	ND	ND	ND	ND	79	25	ND
plus Mathew et al (2000) ³¹	VPT 300	IV	ND	ND	CL	ND/ND/ND	89	40	66	ND	ND	ND	73	ND	ND	ND	ND	ND	ND	ND	ND
plus Trainer et al (1999) ⁵²	NOX 50%	INH	OXY 100%	INH	ED	R/DB/ND	86	31	10	12	ND	ND	70	8	ND	ND	ND	ND	20	83	ND
plus Krusz et al (2000) ⁵³	PPF 110	IV	ND	ND	CL	ND/ND/ND	ND	ND	77	ND	82	ND	100	ND	96	ND	ND	ND	ND	ND	ND
plus Miller et al (2007) ¹⁰	OCT 0.1	IV	CPZ 10	IV	ED	R/DB/P	75	30	24	20	ND	ND	57	90	75	90	ND	ND	46	10	ND
plus Bell et al (1990) ¹⁸	LDC 50	IV	CPZ 12.5	IV	ED2	R/SB/ND	79	ND	26	24	8	33	50	80	29	89	ND	ND	42	21	29

Superior performance is indicated by boldface; if treatment 1 superior, it is also underlined; if treatment 2 superior, it is also italicized. CL = clinic; CPZ = chlorpromazine; DB = double blind; DHE = dihydroergotamine; DMH = dimenhydrinate; ED = emergency department; G1 = group 1; G2 = group 2; IM = intramuscular; INH = inhalation; IV = intravenous; KET = ketorolac; MEP = meperidine; MTC = methotrimprazine; MTC = metoclopramide; OXY = oxygen; P = placebo-controlled; PCB = prochlorperazine; R = randomized; SB = single blind; SQ = subcutaneous; STP = sumatriptan; ND = no data reported.

VALPROATE

Valproate increases γ -aminobutyric acid (GABA) levels in the brain, reduces serotonergic cell activity in the dorsal raphe nucleus, and reduces central activation in the trigeminal nucleus caudalis.⁵⁰ Valproate has also been shown to reduce neurogenic inflammation through GABA_A receptor antagonism.

Mathew et al found that 73% of their patients had substantial headache relief (mild or no pain) 30 minutes after receiving valproate 300 mg IV.⁵¹ There was no control group. Two out of 66 patients reported mild, transient light headedness. Edwards et al compared valproate 500 mg IV to DHE 1 mg IV plus metoclopramide 10 mg IV; headache relief at 4 hours was the same in both groups (60%).⁴⁰ Tanen et al compared valproate 500 mg IV to prochlorperazine 10 mg IV; pain reduction (VAS) at 1 hour was greater for prochlorperazine (-64.5 vs -9.0 ; $P < .01$) with no difference in sedation between the treatments.⁹ Table 4 summarizes the studies involving valproate.

OTHERS: OCTREOTIDE, LIDOCAINE, NITROUS OXIDE, PROPOFOL, AND BUPIVACAINE

Octreotide, a somatostatin analogue, can inhibit neuropeptides that may be involved in headache pathogenesis (prostaglandins, substance P). Miller et al compared octreotide 100 μ g IV to prochlorperazine 10 mg IV; pain reduction (VAS) was greater for prochlorperazine (-50.5 vs -33.3 ; $P < .01$).¹⁰

Intravenous lidocaine has been used to treat neuropathic pain; its mechanism of action involves the blockade of sodium channels. Bell et al compared lidocaine 50 mg IV (repeated up to 150 mg) to chlorpromazine 12.5 mg IV (repeated up to 37.5 mg) and to DHE 1 mg IV (repeated once); pain reduction (11-PPS) was greater with chlorpromazine than lidocaine or DHE (-79.5% vs -50% vs -36.7% ; $P < .05$).¹⁸

Nitrous oxide is a well-known anesthetic, analgesic, and anxiolytic often used in dentistry and surgery. Triner et al compared nitrous oxide (50%) plus oxygen (50%) to oxygen (100%) alone.⁵² A scented mask spray was used to blind the scent of nitrous oxide, which is mildly sweet smelling. Pain reduction (VAS) at 20 minutes was greater for nitrous oxide/

oxygen (-48 vs -6.5 ; $P < .05$). Post-discharge follow up was not done. No side effects were reported.

Propofol is a hypnotic/sedative that acts as a GABA_A receptor agonist and a sodium channel blocker. Krusz et al used open-label propofol to treat 77 patients with intractable headaches.⁵³ Propofol was administered as needed, averaging 110 mg (10 mg/mL), a sub-anesthetic dose. Eighty-two percent of patients were pain free at 30 minutes. Side effects included transient drowsiness or slurred speech, and 8 patients briefly exhibited involuntary finger movements.

Bupivacaine is a long-acting local anesthetic that blocks sodium and potassium channels on pain-signaling neurons. Mellick et al reported on the efficacy of injecting 0.5% bupivacaine 1.5 mL IM bilaterally (3 mL total) 2-3 cm lateral to the spinous process in the lower cervical region (at the 6th or 7th cervical vertebrae).⁵⁴ Complete, rapid pain relief was achieved in 271/417 patients (65.1%), and partial relief was reported by an additional 85 (20.4%). The most common side effect was muscle soreness at the injection site. Table 4 summarizes the studies involving octreotide, lidocaine, nitrous oxide, propofol, and bupivacaine.

DISCUSSION AND CONCLUSIONS

Phenothiazines, as a class, are superior to placebo in providing effective migraine treatment. All 4 studies comparing prochlorperazine to placebo favored prochlorperazine over placebo regardless of the route of delivery (PR, IM, and IV). In the 2 conflicting studies comparing chlorpromazine to placebo, one found chlorpromazine to be clearly superior to placebo, but in the second study, it outperformed placebo only in terms of a reduced need for rescue medication.

Prochlorperazine outperformed ketorolac, magnesium, valproate, octreotide, and sumatriptan. Among the neuroleptics, prochlorperazine was more rapidly effective than promethazine and superior to metoclopramide as a single agent in providing pain relief. When prochlorperazine and metoclopramide were combined with diphenhydramine in a separate study, there was no difference in efficacy. Chlorpromazine was superior to meperidine, DHE, and

lidocaine, and similar to sumatriptan in pain relief. No studies directly compared prochlorperazine to chlorpromazine.

In every investigation of the efficacy of promethazine IM, it was combined with meperidine. As a combination therapy, it performed on par with ketorolac, DHE plus metoclopramide, and placebo. Promethazine should not be administered IV or SQ due to the risk of severe tissue injury, including gangrene. Methotrimeprazine, as a single agent, was similar in pain relief to meperidine plus dimenhydrinate.

Adding a small dose of prochlorperazine (3.5 mg) to DHE did not boost pain relief, but it did decrease the side effect of nausea (albeit with some increase in the incidence of sedation and a minimal increase in akathisia).

The most commonly reported adverse events for prochlorperazine were drowsiness (15-18%) and akathisia, sometimes severe (8-46%). For chlorpromazine, the common side effects were drowsiness (70%) and postural hypotension (17-53%), and for methotrimeprazine, drowsiness (52%) was the side effect most commonly reported. Chlorpromazine has some anticholinergic activity that can counteract akathisia.

The percentage pain-free at 2 hours was greater for droperidol (~40%) than placebo (~20%). Both studies comparing droperidol to prochlorperazine resulted in greater pain relief with droperidol, but in 1 study, there was no difference in average pain reduction. No patients given droperidol exhibited QT prolongation, but they did experience anxiety (30%), akathisia (6-13.3%), and drowsiness (6.7-30%). The 1 study comparing haloperidol to placebo showed superior headache relief with haloperidol (80% vs 15%). Sedation and akathisia were reported in 53% of patients taking haloperidol.

Because of black box warnings for prolonged QTc and the common side effects of sedation and akathisia, droperidol and haloperidol should be reserved for use only when other rescue medications fail to relieve headache. Checking the QTc with an ECG before and after treatment, pretreatment with diphenhydramine, trihexyphenidyl, benzotropine, or a benzodiazepine and IV fluids all are recommended.

Metoclopramide is an effective migraine therapy when used alone or in combination with other anti-

migraine medications. It appears to be more effective when delivered IV than when delivered IM or PR. Three of the 4 studies comparing metoclopramide 10 mg IV to placebo found metoclopramide to be superior, but neither metoclopramide 10 mg IM nor metoclopramide 20 mg PR was superior to placebo. Doses greater than 10 mg IV did not increase efficacy. Metoclopramide 20 mg IV/IM as a single agent was inferior to prochlorperazine 10 mg IV/IM as a single agent. Metoclopramide plus diphenhydramine, was superior to sumatriptan in percentage of patients pain-free to at 2 hours but not at follow up. Six studies compared the commonly used combination of metoclopramide plus DHE and found this combination superior in pain relief to ketorolac as well as meperidine plus hydroxyzine (2 studies). Metoclopramide plus DHE was similar to DHE alone, butorphanol, valproate, and meperidine plus promethazine. The most commonly reported adverse events for metoclopramide were akathisia (8-32%), drowsiness (13-17%) and dizziness (8%).

The studies on antihistamines were not designed to determine the efficacy of the antihistamines as single agents. There are insufficient studies to enable accurate comparisons between an agent paired with an antihistamine vs that agent used alone. More specifically, it remains unknown whether the addition of an antihistamine boosts the analgesic effect of other agents. In the 1 trial in which an antihistamine was compared with placebo, hydroxyzine was not superior to placebo for migraine without aura. When it was combined with another agent, the combination did not increase the pain efficacy of that agent. The data suggest, however, that hydroxyzine might be effective for pain relief in migraine with aura, and a sufficiently powered study comparing hydroxyzine to placebo for migraine with aura is needed.

Granisetron did not outperform placebo in the 1 study included here. This result is similar to those of previous clinical trials involving 5HT₃ antagonists.⁵⁵ The 5HT₃ receptors are involved in pain perception and vomiting. It was hoped their antagonists would be effective both in preventing and aborting migraine by blocking the neurogenic dural inflammation, but they demonstrate substantial effectiveness only as antiemetics . . . not as pain relievers.

Only 3 studies have been conducted to evaluate valproate in the emergent setting for migraine relief, and one of these had no comparison arm. Of the remaining 2 studies, one was open label. In no study was valproate's efficacy compared with placebo. Valproate performed as well as metoclopramide combined with DHE and was inferior to prochlorperazine. Valproate has a favorable side effect profile with no sedation, no negative interactions with triptans or DHE, and no cardiovascular side effects. It is contraindicated in pregnancy and in patients with hepatic problems.

Neither intravenous octreotide nor lidocaine afforded as much pain relief as the phenothiazines to which they were compared. Inhaled nitrous oxide provided greater headache relief than oxygen alone, but it was not determined if this relief was sustained after emergency department discharge. In uncontrolled studies, propofol IV and local injections of bupivacaine have provided substantial relief of migraine pain. In regards to the latter, local injections are relatively quick to administer and would make a useful addition to ED treatment.

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