Percutaneous Interventional Strategies for Migraine Prevention

Meredith Barad, MD, Jessica Ailani, MD, Sameh M Hakim, MD, Narayan R Kissoon, MD, Nathaniel M Schuster, MD, Percutaneous Interventional Strategies for Migraine Prevention: A Systematic Review and Practice Guideline, *Pain Medicine*, Volume 23, Issue 1, January 2022, Pages 164–188, https://doi.org/10.1093/pm/pnab236

Disclosure

- Last 24 months
  - Sub-I Clinical Trial – Rimegepant for TN (TEVA)
  - Consultant for Sprint PNS systems
- This presentation contains any **off-label and/or investigational uses of drugs or products**.
    - This presentation contains off-label or investigational use of products

Objectives

- To clearly understand the current evidence on appropriate use of percutaneous interventions for migraine patients
- To update management strategies for migraine prevention

Funding

- Grant from the AAPM Foundation to address area of needed consensus in migraine

Question

- For patients requiring migraine prevention is *X* treatment more effective than *saline* in reducing headache days per month, acute medication use per month, and impairment as defined by patient-reported outcomes (PROs)?

Pre-Zoom Panel Convened

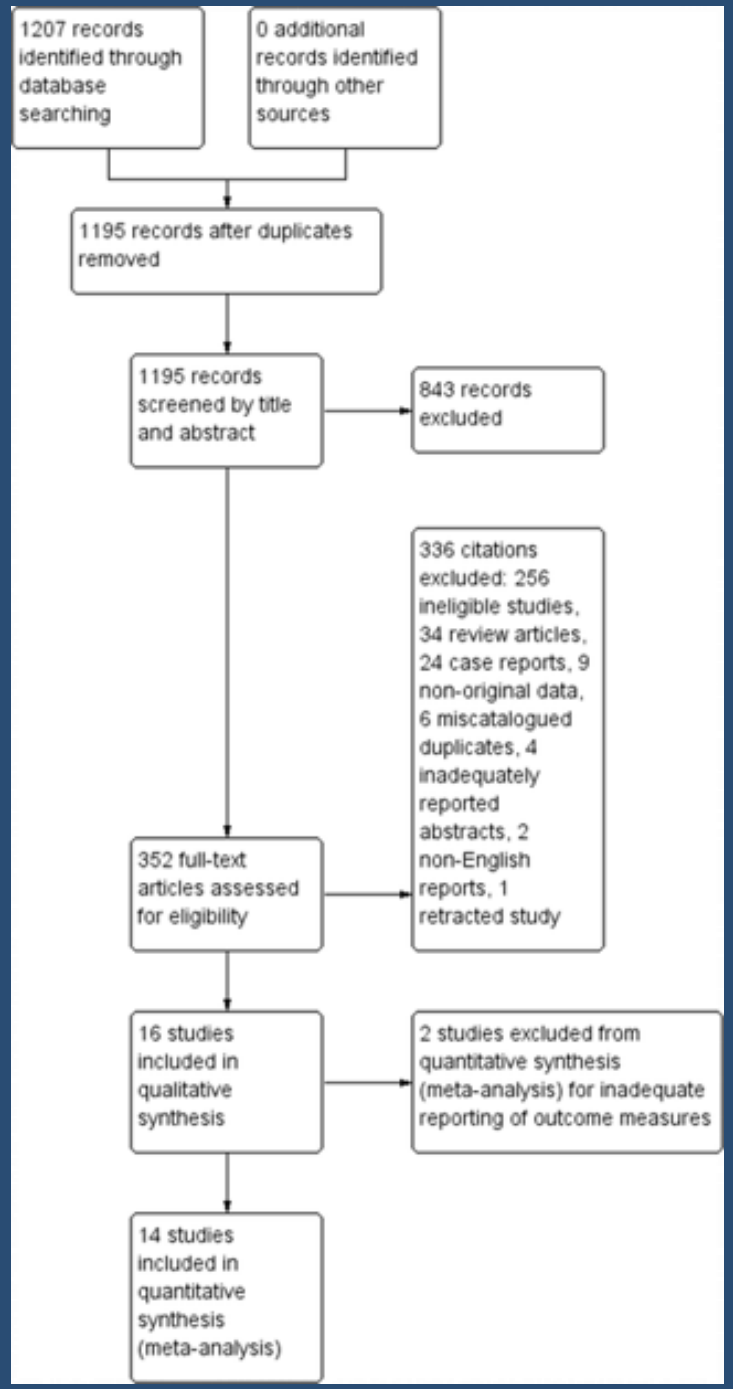
- Chair - Meredith Barad, MD, Stanford Hospital and Clinics, Stanford, California
- Interventional Committee:
- Jessica Ailani, MD, Georgetown University, Washington, DC
- Narayan Kissoon, MD, Mayo Clinic, Rochester, Minnesota
- Nathaniel Schuster, MD, University of California, San Diego, California
- Charles Argoff, MD, Albany Medical College, Albany, New York
- Alexander Feoktistov, MD, Synergy Integrative Headache Center, Chicago, Illinois;
- Teshamae S. Monteith, MD, FAHS, University of Miami, Miami, Florida;
- Amaal Starling, MD, Mayo Clinic-Scottsdale, Scottsdale, Arizona
- Deena Kuruvilla, MD, Westport Headache Institute, Westport, CT
- Don Penzien, PhD, Wake Forest School of Medicine, Winston-Salem, North Carolina
- Elizabeth Seng, PhD, Yeshiva University, Ferkauf Graduate School of Psychology, New York City, New York
- Maisa Ziadni, PhD, Stanford University, Stanford, California
- John Drew Sturgeon, PhD, University of Washington School of Medicine, Seattle, Washington.
- Beth Kurtzweil – patient experience

Patient Population

- Current guidelines on preventive treatments recommend offering prevention for patients with 6 headache (HA) days per month without impairment, 4 HA days per month with some impairment, or 3 HA days per month with severe impairment. (Burch RC et al Neurol Clin 2019;37(4):631–49.)
- We included patients with EM, as defined in studies as patients experiencing <15 HA days per month or<8 migraine days per month, and with CM (15 days per month with 8 days meeting migraine criteria) Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38 (1):1–211

Analytic Process

- Extensive Lit Review -peer reviewed randomized controlled trials (RCTs) comparing any type of interventional treatment with placebo (or sham intervention) in adults (18 years of age or older) with migraine
- 16 studies, all RCTs, were included in qualitative synthesis,
- 2 articles were excluded from quantitative synthesis because of inadequate outcomes reporting
- Quality and Strength of Evidence assesses using Cochran risk of bias
- Certainty of the evidence for each outcome was rated as high, moderate, low, or very low on the basis of study design, risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose response, and plausible confounding factors
- Quantitative synthesis (meta-analysis) could not be conducted for all prespecified outcome measures owing to paucity or inadequate reporting of data. Effect sizes were estimated whenever required metrics were directly reported or could be calculated from a study



Factors weighing into consensus recommendation

- chose outcomes considered important to patients and clinicians
- meta-analysis
- quality of the evidence
- qualitatively reviewed side effects of all treatments
- discussed values and preferences with our patient representative
- included cost analysis when previously discussed by large international bodies (NICE, ICER)

Question 1

- Is chemodenervation via Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol more effective than saline injections in reducing HA days per month, acute medication use per month, and impairment as defined by patient-reported outcomes (PROs)?

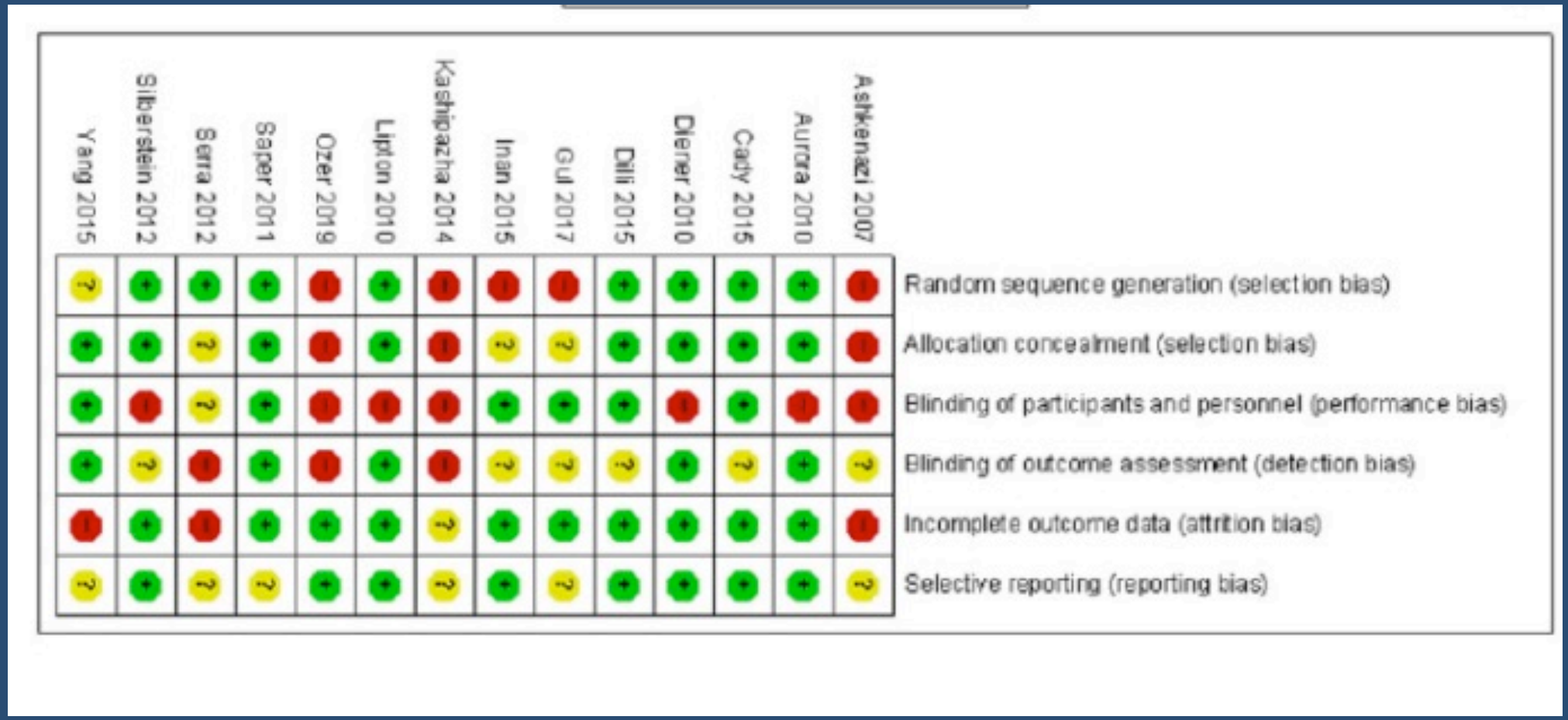
- Meta-analysis of HA days demonstrated a statistically significant difference favoring onabotulinumtoxinA over placebo with a small effect size (Hedges' g = -0.28, 95% CI: -0.41 to -0.15, P < 0.01) with unimportant heterogeneity, low risk of bias, moderate certainty of evidence, patient preference (anecdotal) recommendation of cost effectiveness in CM from NICE and ICER
- STRONG recommendation FOR onabotulinumtoxinA for chronic migraine (CM), and a WEAK recommendation AGAINST onabotulinumtoxinA for episodic migraine (EM)

Study author, n	Diagnostic Criteria	Primary Outcome	Intervention	Follow up	Industry Funded
Aurora et al 2010 n=679 Multicenter RCT	Migraine defined by ICHD-2 ≥ 15 days /month	Change in HA episode frequency (primary outcome was changed prior to unblinding)	OnabotulinumtoxinA per PREEMPT protocol at 0 and 12 weeks	24w	Yes
Diener et al 2010 n=705 Multicenter RCT	Migraine defined by ICHD-2 ≥ 15 days /month	Change in HA day frequency	OnabotulinumtoxinA per PREEMPT protocol at 0 and 12 weeks	24w	Yes
Lipton et al 2011 n= 1384 Multicenter RCT	Migraine defined by ICHD-2 ≥ 15 days /month	Pooled results of PROs: HIT 6, HRQoL MSQ	Onabotulinumtoxin A per PREEMPT protocol at 0 and 12 weeks	24w	Yes

Question 2

- Are greater occipital nerve blocks (GONBs) with local anesthetic (LA) more effective than saline injections in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?
- WEAK recommendation FOR the use of GONBs in CM, insufficient evidence for EM
- Meta-analysis for the outcome of HA day reduction in these two studies significantly favored GONBs with a large and significant effect size (Hedges' g = 0.87, 95% CI ¼ -1.26 to -0.48, P < 0.01), but serious ROB for GUL and INAN, very low certainty of evidence

Study Author	INAN n=84 CM		GUL n=44 CM		Dilli - (negative study) n=70 CM or EM	
	Intervention	Control	Intervention	Control	Intervention	Control
Injectate	1.5 ml of 0.5% bupivacaine diluted in 1 ml of saline	2.5 ml of saline	1.5mL of 0.5% bupivacaine diluted in 1mL of saline	2.5mL of saline	2.5 ml 0.5% bupivacaine plus 0.5 ml 20 mg methylprednisolone	2.75 ml normal saline plus 0.25 ml 1% lidocaine without epinephrine (placebo)
Injection Location	2 cm lateral and 2 cm inferior to the external occipital protuberance in all patients	2 cm lateral and 2 cm inferior to the external occipital protuberance in all patients	2 cm lateral and 2 cm inferior to the external occipital protuberance	2 cm lateral and 2 cm inferior to the external occipital protuberance	the medial third of the distance between the occipital protuberance and the mastoid process.	the medial third of the distance between the occipital protuberance and the mastoid process.
Unilateral or Bilateral	does not state	does not state	Bilateral	Bilateral	79% Bilateral	77% Bilateral
# of Injections	4 weekly GONB with bupi injections for 4 weeks (double-blind phase), then 1 GONB with bupi monthly for 2 months (open-label phase)	4 weekly GONB with saline injections for 4 weeks (double-blind phase), then 1 GONB with bupi monthly for 2 months (open-label phase)	weekly x 4 weeks	weekly x 4 weeks	1	1
Time to Follow Up	4 weeks blinded	4 weeks blinded	4 weeks and 3 months	4 weeks and 3 months	4 weeks	4 weeks
Steroids?	no	no	No	No	Yes	No



Risk of Bias Analysis

Question 3

- Are GONBs with LA and steroid more effective than GONBs with LA alone in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?

- WEAK recommendation AGAINST use of steroid and LA over LA alone for GONBs
- Significant ROB, very low certainty of evidence, risk of steroids (alopecia and fat atrophy)

	Khashipazha n=48 EM or CM		**Ashkenazi n=37 "transformed migraine"**	
	Intervention	Control	Intervention	Control
injectate	1cc of 2% lidocaine with saline (0.5ml), 10mg	1cc of 2% lidocaine with triamcinolone (0.5ml) ? 20mg?	10cc 4.5 ml of lidocaine 2%, 4.5 ml of bupivicaine 0.5%, 1ml of triamcinolone 40mg/mg, 90mg of lidocaine, 2.25 mg of bupivicaine	10cc 4.5 ml of lidocaine 2%, 4.5 ml of bupivicaine 0.5%, 1ml of saline
location	medial third of the distance between the occipital protuberance and the mastoid process.	medial third of the distance between the occipital protuberance and the mastoid process.	2 ml were injected into each GON at the medial third of the distance between the occipital protuberance and the mastoid process. In addition, 0.5 ml was injected into each of the 12 trigger points. The total injected volume was 10 ml	2 ml were injected into each GON at the medial third of the distance between the occipital protuberance and the mastoid process. In addition, 0.5 ml was injected into each of the 12 trigger points. The total injected volume was 10 ml
uni/bi	bilaterally	bilaterally	bilateral	bilateral
# of injections	1	1	1	1
Time to follow up	2weeks, 4 weeks , 8 weeks	2weeks, 4 weeks , 8 weeks	20 min, 4 weeks	20 min , 4 weeks
steroids	no	triamcinolone (mg unknown)	40mg triamcinolone	no
anesthetic	lidocaine	lidocaine	lido/bupi	lido/bupi

Question 6

- Are trigger point injections (TPIs) with LA more effective than saline injections in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?
- INSUFFICIENT evidence to assess the use of TPIs with LA

Question 8

- Is implantable stimulation more effective than sham in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?
- Overall strength for the certainty of evidence for reduction of HA days was moderate with a moderate effect size.
- The strength of certainty of evidence for reduction in acute medication use was very low with a low and nonsignificant effect size,
- and the strength of certainty of evidence for impairment as related to PROs was moderate at 12 weeks with a moderate effect size.
- Although patient satisfaction was high, at least as measured in the ONSTIM trial, this treatment had significantly more AEs than other interventional therapies examined, which, together with higher cost considerations, downgrades the potential net benefit to a WEAK recommendation FOR CM prevention.

Study	Study design, treatment arms	Diagnostic Criteria	Primary Outcome	Secondary Outcome	Intervention/follow up	Funding
Saper et al. 2011 • USA • n=60	Multicenter, randomized, blinded, controlled, feasibility study • Active (n28) • Sham (n16) • Control (n17, plus active intervention in GONB non-responders n5, not included in randomization)	ICHD-2–defined CM, history 12 mo, failed 2 drug classes; HA characteristics: pain C3 to vertex, any location between ears (i.e., occipital or suboccipital region within distribution of greater and/or lesser occipital nerves); positive ONB	No primary outcome (feasibility study): HA reduction days per month • NRS decrease, responder rate (i.e., percentage of patients w/ 50% drop in HA days per month or 3-point drop in overall pain intensity from baseline)		ONS: Medtronic model 7427 Synergy and model 7427V Synergy Versitrel IPGs, model 3487A Pisces Quad and model 3887 Pisces Quad-Compact leads Pulse amplitude: 0–10.5V Frequency: 3–130 H Hz Pulse width: 60–450 ms either 1 or 2 leads Goal: stimulation covers area of HA pain 1 month, 3 month	Industry
Silberstein et al. 2012 • USA • n=157	Multicenter, RCT, • Active intervention (n105) • Sham (n52)	ICHD-2–defined CM, failed 2 acute and 2 preventive medications, positive occipital stimulator trial	Mean daily pain intensity (VAS) from patient diary	HA days reduction (duration 4 h, peak intensity moderate or severe), MIDAS, patient reported HA pain relief (categorical and percentage),	PNS of GON: IPG Genesis St Jude Medical Neuromodulation 12 weeks	Industry

Dodick DW, Silberstein SD, Reed KL, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Long-term results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2015;35(4):344-358.

- Headache days were significantly reduced by 6.7 (±8.4) days in the ITT population ($p<0.001$) and by 7.7 (±8.7) days in the ICM population ($p<0.001$).
- The percentages of patients who achieved a 30% and 50% reduction in headache days and/or pain intensity were 59.5% and 47.8%, respectively.
- MIDAS and Zung PAD scores were significantly reduced for both populations.
- Excellent or good headache relief was reported by 65.4% of the ITT population and 67.9% of the ICM population. More than half the patients in both cohorts were satisfied with the headache relief provided by the device.
- A total of 183 device/procedure-related adverse events occurred during the study, of which 18 (8.6%) required hospitalization and 85 (40.7%) required surgical intervention; 70% of patients experienced an adverse event.

Summary of Recommendations

Table 3. Summary of Recommendations

PICO Question	Recommendation for Migraine Prevention*
1. Is chemodenervation via Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol more effective than saline injections in reducing HA days per month, acute medication use per month, and impairment as defined by patient-related outcomes (PROs)?	STRONG recommendation FOR onabotulinumtoxinA for chronic migraine (CM), and a WEAK recommendation AGAINST onabotulinumtoxinA for episodic migraine (EM)
2. Are greater occipital nerve blocks (GONBs) with local anesthetic (LA) more effective than saline injections in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?	WEAK recommendation FOR the use of GONBS in CM, insufficient evidence for EM
3. Are GONBs with LA and steroid more effective than GONBs with LA alone in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?	WEAK recommendation AGAINST use of steroid and LA over LA alone for GONBs
4. Are other or combined peripheral nerve blocks with LA more effective than saline injections in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?	WEAK recommendation FOR GON + SON blocks
5. Are sphenopalatine ganglion (SPG) blocks with LA more effective than saline injections in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?	WEAK recommendation FOR SPG block in CM
6. Are trigger point injections (TPIs) with LA more effective than saline injections in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?	INSUFFICIENT evidence to assess the use of TPIs with LA
7. Are cervical spine percutaneous interventions more effective than sham interventions in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?	WEAK recommendation FOR pulsed radiofrequency (PRF) of the third occipital nerve (TON)
8. Is implantable stimulation more effective than sham in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?	WEAK recommendation FOR CM prevention
9. Is intrathecal medication more effective than placebo in reducing HA days per month, acute medication use per month, and impairment as defined by PROs?	STRONG recommendation AGAINST

*Unless specified recommendation if for migraine prevention, not subtyped.

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