Nonpharmacologic Treatments for Chronic and Episodic Migraine: A Systematic Review and Meta-Analysis

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Background: Minimally invasive techniques for treatment-resistant migraine have been developed on recent insights into the peripheral pathogenesis of migraines. Although there is a growing body of evidence supporting these techniques, no study has yet compared the effects of these treatments on headache frequency, severity, duration, and cost.

Methods: PubMed, Embase, and Cochrane Library databases were searched to identify randomized placebo-controlled trials that compared radiofrequency ablation, botulinum toxin type A (BT-A), nerve block, neurostimulation, or migraine surgery to placebo for preventive treatment. Data on changes from baseline to follow-up in headache frequency, severity, duration, and quality of life were analyzed.

Results: A total of 30 randomized controlled trials and 2680 patients were included. Compared with placebo, there was a significant decrease in headache frequency in patients with nerve block ($P = 0.04$) and surgery ($P < 0.001$). Headache severity decreased in all treatments. Duration of headaches was significantly reduced in the BT-A ($P < 0.001$) and surgery cohorts ($P = 0.01$). Quality of life improved significantly in patients with BT-A, nerve stimulator, and migraine surgery. Migraine surgery had the longest lasting effects (11.5 months) compared with nerve ablation (6 months), BT-A (3.2 months), and nerve block (11.9 days).

Conclusions: Migraine surgery is a cost-effective, long-term treatment to reduce headache frequency, severity, and duration without significant risk of complication. BT-A reduces headache severity and duration, but it is short-lasting and associated with greater adverse events and lifetime cost. Although efficacious, radiofrequency ablation and implanted nerve stimulators have high risks of adverse events and explantation, whereas benefits of nerve blocks are short in duration. *(Plast. Reconstr. Surg.* 152: 1087, 2023.)

Migraine headache is a widespread debilitating neurologic condition, affecting 14.4% of the worldwide population, and is the leading cause of disability in young women.[1,2] It is best conceptualized as a chronic neurologic disease punctuated by attacks of headache and accompanying symptoms—such as photophobia, phonophobia, nausea, vomiting, and aura—that cause great burden on health, quality of life, productivity, and financial security.[3] Thus, therapies for mitigation of its clinical sequelae are of utmost importance.

Treatment of migraine headaches has largely focused on behavioral and pharmacologic interventions. In addition to modification of lifestyle and environmental factors, migraine

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management includes acute therapies for rapid symptom relief and preventive therapies to reduce the frequency and severity of migraine attacks. The wide range of medications available for migraine headache prophylaxis and abortive treatment underscore the fact that the pathophysiology of migraine headache is still poorly understood. Although significant progress has been achieved in the area of migraine headache management, there still exists a distinct population of patients who do not receive adequate benefit from current treatment strategies and are considered "refractory" to the standard of care.[4]

Multiple contemporary treatments for treatment-resistant migraine patients have been developed based on recent insights into the pathogenesis of migraine headache, which argue against a sole central vasogenic cause and support additional peripheral mechanisms involving compressed or irritated craniofacial nerves that contribute to the generation of migraine headache. For example, the emergence of neuromodulation devices and radiofrequency ablation therapy have sparked interest in their applications in migraine therapy.[5–9] In addition, botulinum toxin type A (BT-A) injection and nerve blocks are relatively new treatment approaches with demonstrated efficacy that support a peripheral mechanism.[10,11] Patients for whom optimal medical management fails and who then experience amelioration of headache after injection at specific anatomical locations can be considered for subsequent surgery to deactivate the trigger sites. Migraine surgery is an exciting prospect for appropriately selected patients with migraine headache and will continue to be a burgeoning field with additional investigative opportunities.[12–14]

This wide spectrum of novel treatments provides a variety of potential options, which may result in uncertainty for choosing an intervention. Although previous studies have examined these novel treatment options in isolation, these studies failed to stratify outcomes by treatment, used studies without randomized placebo groups, examined treatments only at a single site, or did not consider other measures of efficacy besides headache frequency.[8,14–17] Thus, this study is the most rigorous analysis, with only randomized controlled trials (RCTs), and the first to compare the effectiveness of these contemporary treatments for migraine based on changes in the frequency, duration, and severity of migraines and quality of life in adults.

PATIENTS AND METHODS

Data Sources and Searches

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Fig. 1). EMBASE (including Epub Ahead of Print, In-Process & Other NonIndexed Citations), PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were searched from database inception to August 1, 2022. Additional studies were identified and included for analysis by examining the references of existing systematic reviews/meta-analyses, clinical trial registries, and relevant primary studies.

Study Selection

Eligible studies were screened to consist of: (1) RCTs; (2) adult patients (≥18 years) with episodic or chronic migraine; (3) evaluation of radiofrequency ablation, BT-A, nerve block, nerve stimulator, or nerve decompression/deactivation surgery for treatment of migraine; (4) comparisons of the intervention with placebo within the study period; and (5) at least 8-week follow-up in BT-A and 4-week follow-up in other treatments according to standardized guidelines.[18] Migraine headaches for each included study were confirmed to fit the current *International Classification of Headache Disorders*, Third Edition, criteria for either episodic (<15 headaches per month) or chronic (≥15 headaches per month) migraine.[3] Studies that were nonrandomized, open-label, retrospective, non–placebo-controlled studies, or without sufficient data (ie, no reported standard deviations) were excluded. In addition, studies without a well-defined migraine population or those including other headache disorders, such as tension headaches, chronic daily headache, dystonia, and all secondary headaches, were excluded.

Data Extraction and Quality Assessment

Two authors (I.A.C. and M.W.W.) independently performed screening, review, and data extraction of the selected articles. Conflicts between the reviewers were resolved by a third senior investigator (B.G.). A standardized data extraction form was developed to extract study characteristics. Authors were contacted for missing or incomplete information.

The risk of bias of the included RCTs was evaluated with the Cochrane Collaboration's Risk of Bias 2 tool[19] and the Jadad Scale,[20] with excellent interrater agreement (intraclass correlation coefficient, 0.88 to 0.97). Disagreements were

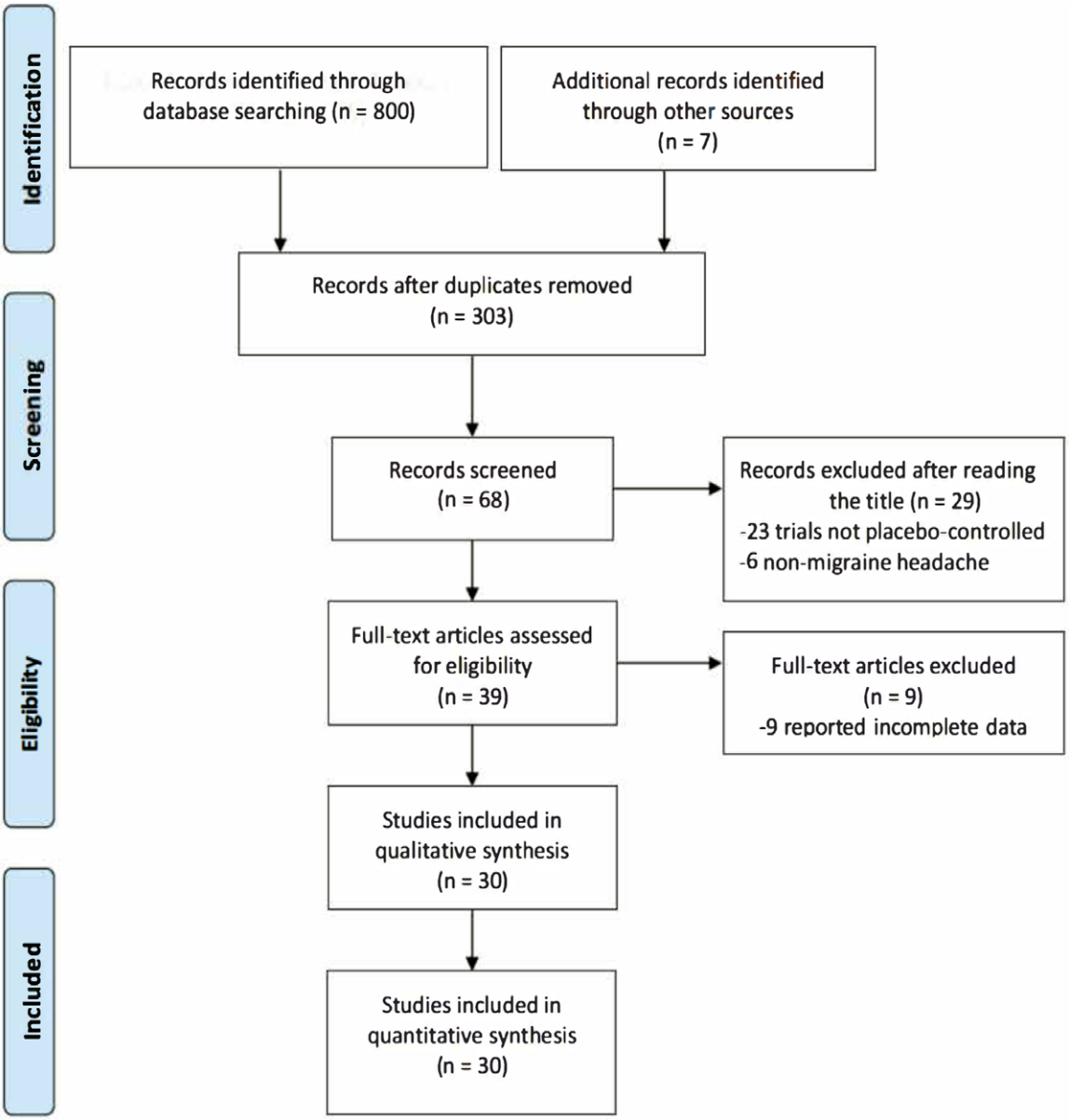

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, literature search, and selection process.

resolved by consensus. In addition, the effect of study sponsorship and use of intention-to-treat analysis for trials with loss to follow-up were evaluated. Publication bias was assessed using the methods of Peters et al.[21] for dichotomous and Egger et al.[22] for continuous outcomes. Potential sources of heterogeneity were identified using stratified analysis and meta-regression.[23] Analysis of the association of placebo with headache outcomes was performed using random-effects meta-regression.

Outcome Measures

The primary outcome was the difference in the number of headache episodes per month from baseline to follow-up. Headache severity, intensity (visual analogue scale, ranging from 0 to 10),[24] duration, analgesic use, adverse events (using the definitions in the original studies), and quality of life [Headache Disability Inventory (HDI),[25] Beck Depression Inventory (BDI),[26] Headache Impact Test (HIT-6),[27] Migraine Disability Assessment Test (MIDAS),[28] Migraine-Specific Quality of Life (MSQ),[29] and Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)[30]]. For the MSQ and SF-36, a higher score indicates improved quality of life; for the HDI, BDI, HIT-6, and MIDAS, a lower score indicates less headache-related disability.

Data Synthesis and Analysis

All statistical analyses for RCTs analyzed participants according to their original allocation group. For crossover RCTs, outcomes were established as the measurements of the cohort before crossover with another treatment to prevent carryover effect. For primary outcome analysis, the number of headache days per month using weighted mean differences was preferentially abstracted and pooled in a random-effects model. For studies that did not provide the standard deviations as a difference between baseline and follow-up, the standard deviation was calculated according to the formula for variance of change: $V(X\text{-}Y) = V(X) + V(Y) - 2 \times cov(X, Y)$, where $cov(X, Y) = r \times SD(X) \times SD(Y)$, r was fixed at 0.5 as per standardized protocol, and $V(X)$ was the variance at baseline and $V(Y)$ was the variance at follow-up.[18] Studies were pooled using an inverse-variance weighted estimation. For studies with more than one treatment group, distinct cohorts were recorded separately and pooled for analysis according to the Cochrane recommendation.[31]

Heterogeneity was assessed visually with forest plots and statistically with the Cochran Q heterogeneity statistics and Higgins I^2.[32] Studies with a value of $P < 0.1$ or $I^2 > 50\%$ were determined to have statistical heterogeneity, prompting random-effect modeling.

All studies, including those using measures other than headache frequency, were secondarily examined by calculating an effect size by means of mean difference. For adverse events, risk ratio was calculated. Treatment groups without data for an outcome of interest were not included for comparison for that outcome. Statistical significance was determined as $P < 0.05$.

All analyses were performed by using R software version 4.1.2. In creating our forest plots, the size of the box for each study was proportional to the contribution of each study to the pooled summary, as by convention.

RESULTS

Radiofrequency Ablation

Of the two included studies, there were 85 patients who were treated with nerve ablation, with a mean age of 42.4% and 51.8% being female, and 40 control patients (Table 1).[7,13,33–60]

There was no significant difference in the number of headache days ($P = 0.21$), although there was a significant reduction in severity by 1.90 (95% CI, 1.36 to 2.43; $P = 0.02$). (**See Figure, Supplemental Digital Content 1**, which shows forest plot of changes in headache episodes per month between baseline and follow-up. *MD*, mean difference, ***http://links.lww.com/PRS/G221***. **See Figure, Supplemental Digital Content 2**, which shows forest plot of changes in headache severity between baseline and follow-up, ***http://links.lww.com/PRS/G222***.) No included studies reported migraine duration or changes in analgesic use. (**See Figure, Supplemental Digital Content 3**, which shows forest plot of changes in headache duration between baseline and follow-up, ***http://links.lww.com/PRS/G223***.) There was no significant difference in MIDAS scores after treatment ($P = 0.12$) (Table 2) or adverse events ($P = 0.07$) compared with the control cohort. (**See Figure, Supplemental Digital Content 4**, which shows forest plot of changes in adverse events between baseline and follow-up. *AE*, adverse events, ***http://links.lww.com/PRS/G224***.)

Nerve Block

Of the four included studies, there were 137 patients who were treated with nerve block, with a mean age of 38.9 years and 81.5% of whom were women, and 113 control patients.[36–39] Treatment regimens and patient demographics for each study are described in Table 1.

Compared with placebo, there was a significant difference in headache days of 5.69 days (95% CI, 0.37 to 11.01 days; $P = 0.04$). Analysis of severity, which was reported in three of the four papers, also revealed a significant decrease in severity of headaches of 1.62 (95% CI, 0.42 to 2.82; $P = 0.01$). The duration of headache episodes was not significantly changed in the two studies of nerve block ($P = 0.24$). There were no studies in our analysis for nerve block that reported quality-of-life scores (Table 2). There were no significant differences in the four studies with reported adverse events when compared with placebo treatments ($P = 0.97$). There were no changes in analgesic use ($P = 0.46$). (**See Figure, Supplemental Digital Content 5**, which shows forest plot of changes in analgesic use between baseline and follow-up, ***http://links.lww.com/PRS/G225***.) The effects lasted 12.1 days on average.

Botulinum Toxin Type A

Our analysis included 10 studies in which patients underwent injection for migraine with a total of 1857 treatment patients and 1499 control patients with saline injections.[40–49] The mean age of the treatment cohort was 40.5 years, and 85% were women. Treatment details, including site of injection and amount of BT-A, are provided in Table 1.

Table 1. Randomized Controlled Trials on Nerve Ablation, Nerve Block, BT-A, Nerve Stimulator, and Migraine Surgery Included in the Meta-Analysis

Reference	Location	Duration (wk)	Sample Size	Treatment Protocol	Treatment Site	Dropouts (%)
Nerve ablation						
Yang et al., 2015[33]	China	24	20 treatment 20 placebo	42°C, 120 sec, twice	Cervical 2–3 posterior medial branches	5 (11.1)
Cohen et al., 2017[34]	United States	24	25 treatment 20 placebo	42°C, 120 sec, three times	Greater and lesser occipital nerves	5 (10)
Nerve block						
Inan et al., 2015[35]	Turkey	4	39 treatment 33 placebo	1.5 mL of 0.5% bupivacaine	Occipital	12 (14.3)
Dilli et al., 2014[36]	United States/ Canada	4	33 treatment 30 placebo	2.5 mL of 0.5% bupivacaine and 0.5 mL of 20 mg methylprednisolone	Occipital	6 (8.7)
Özer et al., 2018[37]	Turkey	11	43 treatment 28 placebo	1 mL of lidocaine	Occipital, supraorbital	16 (18.4)
Gul et al., 2017[38]	Turkey	16	22 treatment 22 placebo	1.5 mL of 0.5% bupivacaine	Occipital	0 (0)
BT-A						
Aurora et al., 2010[39]	United States	24	341 treatment 338 placebo	155–195 U	Frontalis, masseter, temporal, occipital, cervical, paraspinal, trapezius	88 (13.0)
Diener et al., 2010[40]	United States	24	347 treatment 358 placebo	155–195 U	Frontalis, procerus, corrugator, temporal, occipital, cervical, paraspinal, trapezius	60 (8.5)
Hou et al., 2015[41]	China	16	83 treatment 19 placebo	25 U	Frontalis, temporal, occipital, trapezius, procerus, occipital, auriculotemporal, lesser occipital	0 (0)
Chankrachang et al., 2011[42]	Thailand	12	84 treatment 19 placebo	48 or 96 U	Frontalis, temporal, occipital	9 (7)
Evers et al., 2004[43]	Germany	12	40 treatment 20 placebo	100 or 16 U	Frontalis, temporal, cervical, paraspinal, trapezius, sternocleidomastoid	0 (0)
Aurora et al., 2006[44]	United States	270	187 treatment 166 placebo	105–260 U	Frontalis, procerus, corrugator, temporal, occipital, cervical, paraspinal, trapezius, sternocleidomastoid	7 (1.9)
Petri et al., 2009[45]	Germany	12	64 treatment 63 placebo	80 or 210 U	Frontalis, corrugator, temporal, trapezius, sternocleidomastoid	5 (3.9)
Elkind et al., 2006[46]	United States	16	312 treatment 106 placebo	7.5, 25, or 50 U	Frontalis, procerus, corrugator, temporal	102 (24.4)
Relja et al., 2007[47]	Croatia	12	377 treatment 118 placebo	75, 150, or 225 U	Frontalis, procerus, corrugator, temporal, lesser occipital, cervical, paraspinal, trapezius, sternocleidomastoid	20 (3.9)
Hollanda et al., 2014[48]	Brazil	12	20 treatment 18 placebo	100 U	Frontalis, temporal, occipital	0 (0)
Nerve stimulator						
Zhang et al., 2021[49]	China	4	33 treatment 26 placebo	Transcutaneous	Vagus nerve	11 (15.7)
Diener et al., 2019[50]	Germany	4	165 treatment 167 placebo	Noninvasive	Vagus nerve	145 (30.4)

(*Continued*)

Table 1. *Continued*

Reference	Location	Duration (wk)	Sample Size	Treatment Protocol	Treatment Site	Dropouts (%)
Mekhail et al., 2017[51]	United States	4	14 treatment 6 placebo	Implanted	Occipital nerve	0 (0)
Saper et al., 2011[52]	United States	12	49 treatment 17 placebo	Implanted	Occipital nerve	0 (0)
Silberstein et al., 2016[7]	United States	8	30 treatment 29 placebo	Noninvasive	Vagus nerve	0 (0)
Juan et al., 2016[53]	China	12	40 treatment 40 placebo	Percutaneous	Mastoid	0 (0)
Kumar et al., 2020[54]	India	4	10 treatment 10 placebo	Transmagnetic	Left motor cortex	0 (0)
Rocha et al., 2015[55]	Brazil	12	10 treatment 9 placebo	Transcranial	Visual cortex	0 (0)
Schoenen et al., 2013[56]	Brussels	12	34 treatment 33 placebo	Transcutaneous	Supratrochlear, supraorbital nerves	0 (0)
Li et al., 2017[57]	China	12	31 treatment 31 placebo	Percutaneous	Occipitotemporal nerves	0 (0)
Migraine surgery						
Guyuron et al., 2005[58]	United States	52	89 treatment 19 placebo	Removal of the glabellar muscles, zygomatico-temporal branch of the trigeminal nerve, semi-spinalis capitis muscle, or septoplasty and/or turbinectomy	Frontal, temporal, occipital, or nasal trigger sites	17 (13.6)
Bajaj et al., 2021[59]	India	24	13 treatment 13 placebo	Removal of the glabellar muscles, zygomatico-temporal branch of the trigeminal nerve, semi-spinalis capitis muscle, or septoplasty and/or turbinectomy	Frontal, temporal, occipital, or nasal trigger sites	0 (0)
Omranifard et al., 2016[60]	Iran	52	34 treatment 16 placebo	Removal of the glabellar muscles, zygomatico-temporal branch of the trigeminal, or greater and lesser occipital nerves	Frontal, temporal, or occipital trigger sites	0 (0)

Table 2. Standardized Mean Differences in Quality-of-Life Scores from Baseline to Follow-Up

Treatment and Scale	SMD	*P*
Nerve ablation		
Migraine Disability Assessment	1.13	0.12
Nerve block		
None reported		
BT-A		
Beck Depression Inventory	0.02	0.99
Headache Depression Inventory	−6.41	0.30
Headache Impact Test	−2.4	<0.006[a]
Migraine Disability Assessment	0.41	<0.001[a]
Nerve stimulator		
Migraine Disability Assessment	4.3	0.27
Migraine-Specific Quality of Life	2.3	0.48
Medical Outcomes Study 36-Item Short-Form Health Survey	7.0	<0.001[a]
Migraine surgery		
Migraine Disability Assessment	34.2	0.08[b]
Migraine-Specific Quality of Life (emotional)	34.3	<0.001[a]
Migraine-Specific Quality of Life (preventive)	28.6	<0.001[a]
Migraine-Specific Quality of Life (restrictive)	13.9	0.63
Medical Outcomes Study 36-Item Short Form Health Survey (mental)	6.9	<0.001[a]
Medical Outcomes Study 36-Item Short Form Health Survey (physical)	1.61	0.70

SMD, standardized mean difference.
[a]Statistically significant.
[b]Approaching statistical significance.

There was no significant difference noted in our primary outcome of headache days in the BT-A treatment compared with placebo ($P = 0.1$), although there was a significant decrease in severity of 2.92 (95% CI, 1.30 to 4.54; $P < 0.001$) and headache duration by 4.58 days (95% CI, 2.26 to 6.90 days; $P < 0.001$). MIDAS was the only quality-of-life scale with significant changes for treatment with BT-A compared with placebo ($P < 0.001$). BDI, HDI, and HIT-6 were also reported, but did not demonstrate statistically significant differences (Table 2). There was a significant increase in adverse effects in the BT-A cohort versus the placebo cohort of 0.6 event (95% CI, 0.32 to 0.88 event; $P < 0.001$). There was a trend toward decreased monthly analgesic use, although it failed to reach statistical significance ($P = 0.05$). Effects lasted 3.2 months on average.

Nerve Stimulator

There were 10 studies on nerve stimulator, with 416 patients in the nerve stimulator cohort and 368 patients in the placebo group.[7,50–58] The mean age for patients who underwent nerve stimulator treatment was 30.3 years, and 82.5% of them were women. Patient demographics and treatment protocols for each study can be found in Table 1.

There were no significant changes in headache days ($P = 0.07$) or duration ($P = 0.44$), although there was a significant decrease in headache severity of 1.8 (95% CI, 0.05 to 3.55; $P = 0.04$). In studies examining treatment with nerve stimulator, only quality-of-life outcomes collected by means of the SF-36 were statistically significantly different from placebo ($P < 0.001$), whereas the MIDAS and MSQ outcomes were comparable to placebo (Table 2). There were no significant differences in analgesic use or adverse events overall ($P = 0.15$). Implanted stimulators were associated with significantly more adverse events than noninvasive stimulators ($P < 0.001$), with an explantation rate of 53.6%. Average effect duration was not available in nerve stimulator studies, as implanted nerve stimulators had a preset firing rate irrespective of patient-reported symptom resolution.

Surgical Interventions

Of the four included studies on surgical treatment for migraine headaches, there were 185 patients in the treatment group and 74 patients who received placebo.[13,59–61] The mean age of the treatment cohort was 42.5 years and 69.2% were women. In the treatment group, an average of 1.85 trigger sites ($n = 185$) were operated on. Patient demographics and information detailing surgical technique can be found in Table 1.

There was a significant reduction in the number of headache days of 6.02 days (95% CI, 4.03 to 8.02 days; $P < 0.001$), severity by 2.47 (95% CI,

0.36 to 4.58; $P = 0.02$), and duration of headache by 0.44 days (95% CI, 0.13 to 0.74 day; $P = 0.01$). Six quality-of-life scales were collected in patients treated with surgery, of which MSQ preventive and emotional and SF-36 were significantly improved after treatment compared with placebo ($P < 0.001$ and $P < 0.001$, respectively) (Table 2). There were significantly fewer workdays lost in the surgery cohort than in the sham cohort (1.5 days; $P < 0.001$). There was no significant difference in adverse events ($P = 0.07$) in comparison with the control cohort. No included studies reported analgesic use in surgical treatment for migraine headaches.

Study Bias

Funnel plots were created to evaluate for potential small-study bias in the analyzed studies. (**See Figure, Supplemental Digital Content 6**, which shows funnel plot for headache frequency. Funnel plots demonstrated no evidence of asymmetry or small-study bias for all included outcomes ***http://links.lww.com/PRS/G226***.) We found no evidence of publication bias for all outcomes (Egger method, $P = 0.21$).

DISCUSSION

Treatments for refractory and intractable migraine have been of growing interest, particularly given the diversity and utility of novel treatments. Nerve stimulators, nerve blocks, BT-A, and surgery for migraine headache all offer new avenues for patients who do not sufficiently respond to conventional therapies or tolerate the side effects of medications. However, there have been no studies that have analyzed and compared outcomes for each of these treatments. Furthermore, although headache frequency is an important factor that is often analyzed, headache intensity and duration are essential aspects of migraine treatment inherent in quality of life, but are underreported.[6,16–18] In our analysis, we found that migraine surgery is the only treatment of the four novel options that has been documented to reduce the frequency, severity, and duration of migraine headaches.

The pathophysiology of migraine headaches has been under debate, with proposed mechanisms for both peripheral and central causes. Injection of BT-A leads to chemical deactivation of peripheral nerve-triggering elements, thus diminishing inciting stimuli for migraine attacks. In addition, nerve blocks containing long-acting corticosteroids produce effects lasting a few weeks or longer, negating the need for pharmaceutical agents. Because all four of the discussed treatments in this review act on the peripheral nerves, these results strongly support the clinical role of the peripheral mechanism on the onset of the migraine cascade. This theory has been advocated by the senior author (B.G.) over the past 20 years, and has been further validated by the anatomical investigations of Blake and Burstein.[61,62] In contrast, the central mechanism undoubtedly plays a role as well, as evidenced by symptoms such as nausea, vomiting, photophobia, phonophobia, and many others that cannot be explained by the peripheral mechanism alone.

It must be considered that rigorous patient selection is necessary for successful migraine surgery.[63] Researchers and practicing surgeons use the expertise of board-certified neurologists and the diagnostic criteria set forth by the International Headache Society to screen for patients with true migraine headache, as many patients can have overlapping headache diagnoses.[64] In addition, certain types of migraine headaches may respond more favorably to certain treatments. For example, neuromodulators and nerve blocks are typically used for treatment of occipital headaches, as the occipital nerves act as convenient conduits for anesthetic or stimulation delivery to the cervical cord and brainstem.[17,65] However, in the senior author's experience, surgical outcomes are most successful in patients with the ability to self-identify and point to the headache site of origin, detection of a vascular signal on Doppler ultrasound, and a positive response to nerve block, regardless of the diagnostic migraine classification.

Severity and duration of migraine headaches have been cited as the most important measurements of migraine treatment efficacy, which were significantly reduced after both BT-A and migraine surgery in our analysis.[66] However, BT-A did not have a significant effect on decreasing monthly headache days, which may be explained by the protocols used in the included studies. Most trials followed protocols with fixed injection sites that did not adequately address the main peripheral nerve triggers responsible for some forms of migraines. The Phase III Research Evaluating Migraine Prophylaxis Therapy 1 and 2 trials were landmark studies that used "follow the pain" protocols and demonstrated a significant decrease in headache days after BT-A injection but were confounded by ineffective placebo, as up to 85% of patients and researchers were able to decipher group allocation based on visible muscle paralysis.[18,40,41]

Furthermore, the effects of BT-A and nerve bock are temporary, and their use is not without risks. Consistent with previous established findings, our meta-analysis identified BT-A as the only treatment to have a significantly greater incidence of adverse events than placebo. Common side effects included blepharoptosis, diplopia, injection-site pain, and atrophy of the injected muscles, most notably in the temporalis muscles (ie, hourglass deformity).[67,68] Degradation of these chemical products results in resistance to blockage and often require surgery within months of initiating therapy.[37] Nerve block may better serve as a tool to confirm trigger sites and to evaluate candidacy for migraine surgery rather than as a long-term treatment. Thus, patients who are responders to BT-A and nerve block may benefit from more definitive decompression or deactivation of craniofacial peripheral nerves by surgical techniques, particularly for those who do not sufficiently respond to conventional therapies or tolerate the side effects of medications.[69,70] Surgical removal of impinging or irritating muscles and vessels around the peripheral nerves provides a long-term solution, rather than simply masking pain signals.

Migraine burden and quality of life are other important metrics of treatment effectiveness. Our study analyzed six different questionnaires and 10 different aspects of quality of life, and found significant improvement in BT-A, nerve stimulator, and migraine surgery. Additional homogeneity in reports of migraine burden through quality-of-life studies is encouraged for future studies.

In the era of cost-conscious health care, it is imperative for physicians to consider cost-effectiveness. Although there is a role for nonpharmacologic treatments given their potential for better tolerability, cost and lack of insurance coverage are barriers for many patients. The high complication rate requiring surgical interventions are concerning over the cost-effectiveness and safety of the procedure. In particular, implanted nerve stimulation devices, although effective for selected patients with intractable headache disorders, have been shown to result in an additional 21% of initial costs for hospitalization and hardware explantation surgery in 8.6% and 40.7% of the patients, respectively.[71,72] In a cost analysis study of implanted occipital nerve stimulators for intractable migraine, Mueller et al. found that these complications added nearly 21% to initial costs.[70]

Multiple studies have demonstrated that peripheral trigger-site deactivation surgery is more effective and less costly than BT-A injections, and it is the most cost-effective treatment for refractory migraine headaches.[73,74] The therapeutic effects of BT-A tapers 2 to 3 months after administration, requiring multiple repeated treatments to maintain its efficacy, and some patients may develop resistance to BT-A after some period of positive response. Furthermore, those with nasal/retrobulbar trigger sites either do not respond to BT-A at all, or BT-A may alleviate only some secondary symptoms, such as headaches that extend to the forehead, thus reducing the headache intensity without decreasing headache frequency. The cumulative costs and decreased benefits associated with BT-A injections accrued over a patient's lifetime make this treatment modality significantly less cost-effective than migraine surgery. A study by Schoenbrunner et al. found that the economic value of migraine surgery demonstrates a median total cost reduction of $3950 at 5 years postoperatively, indicating that surgical intervention can lead to significant cost savings by obviating expenses associated with medications, doctor visits, and other financial burdens relating to migraine headache.[73,74]

Radiofrequency ablation is another prospect that may offer temporary benefit for cervicogenic headaches, occipital neuralgia, and potentially migraines, but carries increased postoperative risk. Most studies found improvements in pain symptoms to be short-lived after radiofrequency ablation, lasting up to only 12 weeks.[9,15,35] Cohen et al. demonstrated pulsed radiofrequency initially improved pain scores, but no longer carried significance after 6 months.[34] In addition, long-term outcomes and complications are poorly defined and may be underreported, as no studies have investigated outcomes beyond 1 year.[9,15] Thermal injury from radiofrequency ablation may be responsible for postoperative numbness, worsening headache, and intractable pain caused by intrinsic nerve scarring and neuroma-in-continuity.[9]

We recognize that there are limitations to our study. First, there remains a deficit in the literature of placebo-controlled studies of nonpharmacologic migraine treatment, particularly those of migraine surgery, in which the majority is led by a single author. There is a need for further placebo-controlled studies by different centers to consolidate the efficacy of migraine surgery. Second, nonpain symptoms of migraine, such as nausea, photophobia, and phonophobia, may present with additional burden of disease comparable to that of pain, and are heavily underreported in the literature. In our experience, patients who responded to migraine surgery

experienced either mitigation or complete resolution of both nonpain and pain symptoms. Finally, RCTs compared treatments against placebo, limiting comparative effectiveness inferences between nonpharmacologic treatments. Head-to-head trials of active therapies and trials of combinations of therapies are needed to support shared decision-making among all the available treatment options.

CONCLUSIONS

This report analyzed five contemporary nonmedication treatments for migraine: radiofrequency ablation, BT-A, nerve stimulator, nerve block, and surgical interventions. Of these treatments, only migraine surgery and BT-A significantly improved migraine severity and duration. Migraine surgery represents a cost-effective treatment to reduce headache frequency, severity, and duration without significant risk of complications compared with placebo. BT-A is also effective in reducing severity and duration with improved migraine burden but is associated with significantly more adverse events and greater lifetime cost.

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DISCLOSURE

The authors have no financial interest in any of the products, devices, or drugs mentioned in this article.

REFERENCES

1. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17:954–976.
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204–1222.
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, Third Edition. *Cephalalgia* 2018;38:1–211.
4. D'Amico D, Leone M, Grazzi L, Bussone G. When should "chronic migraine" patients be considered "refractory" to pharmacological prophylaxis? *Neurol Sci.* 2008;29(Suppl 1):S55–S58.
5. Bovim G, Sand T. Cervicogenic headache, migraine without aura and tension-type headache. Diagnostic blockade of greater occipital and supra-orbital nerves. *Pain* 1992;51:43–48.
6. Moisset X, Pereira B, Ciampi de Andrade D, Fontaine D, Lantéri-Minet M, Mawet J. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. *J Headache Pain* 2020;21:142.
7. Silberstein SD, Calhoun AH, Lipton RB, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: the EVENT study. *Neurology* 2016;87:529–538.
8. Evans AG, Horrar AN, Ibrahim MM, et al. Outcomes of transcutaneous nerve stimulation for migraine headaches: a systematic review and meta-analysis. *J Neurol.* 2022;269:4021–4029.
9. Orhurhu V, Huang L, Quispe RC, et al. Use of radiofrequency ablation for the management of headache: a systematic review. *Pain Physician* 2021;24:E973–E987.
10. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. *Headache* 2003;43(Suppl 1):S9–S15.
11. Levin M. Nerve blocks in the treatment of headache. *Neurotherapeutics* 2010;7:197–203.
12. Guyuron B, Tucker T, Davis J. Surgical treatment of migraine headaches. *Plast Reconstr Surg.* 2002;109:2183–2189.
13. Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S. A placebo-controlled surgical trial of the treatment of migraine headaches. *Plast Reconstr Surg.* 2009;124:461–468.
14. ElHawary H, Barone N, Baradaran A, Janis JE. Efficacy and safety of migraine surgery: a systematic review and meta-analysis of outcomes and complication rates. *Ann Surg.* 2022;275:e315–e323.
15. Ducic I, Felder JM III, Fantus SA. A systematic review of peripheral nerve interventional treatments for chronic headaches. *Ann Plast Surg.* 2014;72:439–445.
16. Nagori SA, Jose A, Roychoudhury A. Surgical management of migraine headaches: a systematic review and meta-analysis. *Ann Plast Surg.* 2019;83:232–240.
17. Shauly O, Gould DJ, Sahai-Srivastava S, Patel KM. Greater occipital nerve block for the treatment of chronic migraine headaches: a systematic review and meta-analysis. *Plast Reconstr Surg.* 2019;144:943–952.
18. Bruloy E, Sinna R, Grolleau J-L, Bout-Roumazeilles A, Berard E, Chaput B. Botulinum toxin versus placebo: a meta-analysis of prophylactic treatment for migraine. *Plast Reconstr Surg.* 2019;143:239–250.
19. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
20. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
21. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA.* 2006;295:676–680.
22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
23. Sharp S. Meta-analysis regression. *Stata Techn Bull.* 1998;7:16–24.
24. Kelly A. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emerg Med J.* 2001;18:205–207.
25. Jacobson GP, Ramadan NM, Aggarwal SK, Newman CW. The Henry Ford hospital headache disability inventory (HDI). *Neurology* 1994;44:837–842.
26. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *J Pers Assess.* 1996;67:588–597.

27. Bjorner JB, Kosinski M, Ware JE Jr. Using item response theory to calibrate the headache impact test (HIT) to the metric of traditional headache scales. *Qual Life Res.* 2003;12:981–1002.
28. Bigal ME, Rapoport AM, Lipton RB, Tepper SJ, Sheftell FD. Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. *Headache* 2003;43:336–342.
29. Cole JC, Lin P, Rupnow MF. Validation of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. *Qual Life Res.* 2007;16:1231–1237.
30. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247–263.
31. Higgins JP, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions.* Hoboken, NJ: Wiley-Blackwell; 2019.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.
33. Yang Y, Huang X, Fan Y, Wang Y, Ma K. Efficacy of pulsed radiofrequency on cervical 2-3 posterior medial branches in treating chronic migraine: a randomized, controlled, and double-blind trial. *Evid Based Complement Alternat Med.* 2015;2015:690856.
34. Cohen SP, Peterlin BL, Fulton L, et al. Randomized, double-blind, comparative-effectiveness study comparing pulsed radiofrequency to steroid injections for occipital neuralgia or migraine with occipital nerve tenderness. *Pain* 2015;156:2585–2594.
35. Inan LE, Inan N, Karadaş O, et al. Greater occipital nerve blockade for the treatment of chronic migraine: a randomized, multicenter, double-blind, and placebo-controlled study. *Acta Neurol Scand.* 2015;132:270–277.
36. Dilli E, Halker R, Vargas B, et al. Occipital nerve block for the short-term preventive treatment of migraine: a randomized, double-blinded, placebo-controlled study. *Cephalalgia* 2015;35:959–968.
37. Özer D, Bölük C, Türk Börü U, Altun D, Taşdemir M, Köseoğlu Toksoy C. Greater occipital and supraorbital nerve blockade for the preventive treatment of migraine: a single-blind, randomized, placebo-controlled study. *Curr Med Res Opin.* 2019;35:909–915.
38. Gul HL, Ozon AO, Karadas O, Koc G, Inan LE. The efficacy of greater occipital nerve blockade in chronic migraine: a placebo-controlled study. *Acta Neurol Scand.* 2017;136:138–144.
39. Aurora SK, Dodick DW, Turkel CC, et al.; PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010;30:793–803.
40. Diener HC, Dodick DW, Aurora SK, et al.; PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010;30:804–814.
41. Hou M, Xie J-F, Kong X-P, et al. Acupoint injection of onabotulinumtoxin A for migraines. *Toxins (Basel)* 2015;7:4442–4454.
42. Chankrachang S, Arayawichanont A, Poungvarin N, et al. Prophylactic botulinum type A toxin complex (Dysport) for migraine without aura. *Headache* 2011;51:52–63.
43. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt I-W, Frese A. Botulinum toxin A in the prophylactic treatment of migraine—a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2004;24:838–843.
44. Aurora SK, Gawel M, Brandes JL, Pokta S, Vandenburgh AM; BOTOX North American Episodic Migraine Study Group. Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. *Headache* 2007;47:486–499.
45. Petri S, Tölle T, Straube A, Pfaffenrath V, Stefenelli U, Ceballos-Baumann A; Dysport Migraine Study Group. Botulinum toxin as preventive treatment for migraine: a randomized double-blind study. *Eur Neurol.* 2009;62:204–211.
46. Elkind AH, O'Carroll P, Blumenfeld A, DeGryse R, Dimitrova R; BoNTA-024-026-036 Study Group. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. *J Pain* 2006;7:688–696.
47. Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C; European BoNTA Headache Study Group. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. *Cephalalgia* 2007;27:492–503.
48. Hollanda L, Monteiro L, Melo A. Botulinum toxin type a for cephalic cutaneous allodynia in chronic migraine: a randomized, double-blinded, placebo-controlled trial. *Neurol Int.* 2014;6:5133.
49. Zhang Y, Huang Y, Li H, et al. Transcutaneous auricular vagus nerve stimulation (taVNS) for migraine: an fMRI study. *Reg Anesth Pain Med.* 2021;46:145–150.
50. Diener HC, Goadsby PJ, Ashina M, et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: the multicentre, double-blind, randomised, sham-controlled PREMIUM trial. *Cephalalgia* 2019;39:1475–1487.
51. Mekhail NA, Estemalik E, Azer G, Davis K, Tepper SJ. Safety and efficacy of occipital nerves stimulation for the treatment of chronic migraines: randomized, double-blind, controlled single-center experience. *Pain Pract.* 2017;17:669–677.
52. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ; ONSTIM Investigators. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia* 2011;31:271–285.
53. Juan Y, Shu O, Jinhe L, et al. Migraine prevention with percutaneous mastoid electrical stimulator: a randomized double-blind controlled trial. *Cephalalgia* 2017;37:1248–1256.
54. Kumar A, Mattoo B, Bhatia R, Kumaran S, Bhatia R. Neuronavigation based 10 sessions of repetitive transcranial magnetic stimulation therapy in chronic migraine: an exploratory study. *Neurol Sci.* 2021;42:131–139.
55. Rocha S, Melo L, Boudoux C, Foerster A, Araújo D, Monte-Silva K. Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: a pilot randomized controlled trial. *J Neurol Sci.* 2015;349:33–39.
56. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology* 2013;80:697–704.
57. Li H, Xu QR. Effect of percutaneous electrical nerve stimulation for the treatment of migraine. *Medicine (Baltimore)* 2017;96:e8108.
58. Guyuron B, Kriegler JS, Davis J, Amini SB. Comprehensive surgical treatment of migraine headaches. *Plast Reconstr Surg.* 2005;115:1–9.
59. Bajaj J, Doddamani R, Chandra SP, et al. Comparison of peripheral neurectomy vs. medical treatment for migraine: a randomized controlled trial. *Neurol India* 2021;69(Suppl):S110–S115.

60. Omranifard M, Abdali H, Ardakani MR, Talebianfar M. A comparison of outcome of medical and surgical treatment of migraine headache: in 1 year follow-up. *Adv Biomed Res.* 2016;5:121.
61. Blake P, Burstein R. Emerging evidence of occipital nerve compression in unremitting head and neck pain. *J Headache Pain* 2019;20:76.
62. Larson K, Lee M, Davis J, Guyuron B. Factors contributing to migraine headache surgery failure and success. *Plast Reconstr Surg.* 2011;128:1069–1075.
63. Yi X, Cook AJ, Hamill-Ruth RJ, Rowlingson JC. Cervicogenic headache in patients with presumed migraine: missed diagnosis or misdiagnosis? *J Pain* 2005;6:700–703.
64. Bari AA, Pouratian N. Brain imaging correlates of peripheral nerve stimulation. *Surg Neurol Int.* 2012;3(Suppl 4):S260–S268.
65. Guyuron B. Discussion: botulinum toxin versus placebo: a meta-analysis of prophylactic treatment for migraine. *Plast Reconstr Surg.* 2019;143:251–253.
66. Aurora S. Botulinum toxin type A for the treatment of migraine. *Expert Opin Pharmacother.* 2006;7:1085–1095.
67. Guyuron B, Rose K, Kriegler JS, Tucker T. Hourglass deformity after botulinum toxin type A injection. *Headache* 2004;44:262–264.
68. Guyuron B, Kriegler JS, Davis J, Amini SB. Five-year outcome of surgical treatment of migraine headaches. *Plast Reconstr Surg.* 2011;127:603–608.
69. Kung TA, Guyuron B, Cederna PS. Migraine surgery: a plastic surgery solution for refractory migraine headache. *Plast Reconstr Surg.* 2011;127:181–189.
70. Mueller O, Diener H-C, Dammann P, et al. Occipital nerve stimulation for intractable chronic cluster headache or migraine: a critical analysis of direct treatment costs and complications. *Cephalalgia* 2013;33:1283–1291.
71. 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;35:344–358.
72. Faber C, Garcia RM, Davis J, Guyuron B. A socioeconomic analysis of surgical treatment of migraine headaches. *Plast Reconstr Surg.* 2012;129:871–877.
73. Schoenbrunner AR, Khansa I, Janis JE. Cost-effectiveness of long-term, targeted onabotulinumtoxinA versus peripheral trigger site deactivation surgery for the treatment of refractory migraine headaches. *Plast Reconstr Surg.* 2020;145:401e–406e.
74. Shauly O, Gould DJ, Patel KM. Cost-utility analysis of surgical decompression relative to injection therapy for chronic migraine headaches. *Aesthet Surg J.* 2019;39:NP462–NP470.