Botulinum Neurotoxin for Chronic Migraine and Trigeminal Neuralgia

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Onabotulinumtoxin A is the only botulinum toxin serotype that has been evaluated for the treatment of primary headache disorders. Onabotulinumtoxin A has not been shown to be superior to placebo for the prophylactic treatment of chronic tension-type headache or episodic migraine (headache <15 days per month). However, two recent pivotal studies demonstrated Onabotulinumtoxin A to be superior to placebo and effective and safe for the prophylactic treatment of chronic migraine (CM). These studies led to the regulatory approval of Onabotulinumtoxin A for the prophylactic treatment of CM. This presentation will focus on the evidence-base which supports the efficacy and safety of Onabotulinumtoxin A for the prophylaxis of CM, the injection protocol used in the pivotal studies, and injection tips for practitioners.

Chronic migraine (CM) is a disabling neurologic disorder that affects 1.3% to 2.4 % of the general population.[1-4] Patients with CM experience headache ≥15 days per month for ≥3 months, with headaches occurring on ≥8 days being classified as migraine headaches or headaches that respond to migraine-specific medications.[5] CM is the most common type of primary chronic daily headache (CDH) in headache specialty centers in the United States.[1, 5-7]

The overuse of acute headache medications can be a problem for patients with chronic headache disorders. Most CM patients who seek treatment in tertiary headache clinics overuse acute headache medications.[8] An effective, safe, and well-tolerated prophylactic headache medication will improve the patient's clinical condition and probably reduce acute headache pain medication consumption.[1, 9] Only 33.3% of CM patients use prophylactic headache medication.[1]

OnabotulinumtoxinA has been reported to relieve pain in a variety of conditions, including migraine.[10-22] Efficacy results from previous trials in patients with episodic migraine (generally understood as occurring <15 days per month) have been negative.[12, 23-25] Results from other exploratory trials in episodic migraine, chronic-tension type headache and CDH have been mixed, but have suggested that onabotulinumtoxinA may be useful as preventive treatment for CDH, specifically patients suffering from CM.[10-12, 26-28] Various onabotulinumtoxinA dosages and injection paradigms have been evaluated in these studies,[10-12, 26-28] and the PREEMPT injection protocol evolved from these paradigms. Pivotal results from the PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) clinical program have established onabotulinumtoxinA as a safe, well-tolerated, and effective headache prophylactic CM treatment.[29-31]

Although the exact mechanism of onabotulinumtoxinA in antinociception has not been fully elucidated, animal and human studies indicate that onabotulinumtoxinA inhibits the release of nociceptive mediators, such as glutamate, substance P, and calcitonin gene-related peptide, from

peripheral termini of primary afferents (nociceptors).[32-39] Blocking release of these neurotransmitters inhibits neurogenic inflammation; this, in turn, inhibits peripheral sensitization of nociceptive (pain-conducting) nerve fibers. As a result, peripheral pain signals to the central nervous system are reduced and, indirectly, central sensitization is blocked.[32, 33, 38, 39] . In addition, recent evidence suggests that not only is peripherally injected toxin undergoes axonal transport from peripheral sensory trigeminal afferents to central trigeminal sensory neurons within the trigeminal nucleus caudalis, but that this transport is obligatory for the antinociceptive effect of onabotulinumtoxin A in the trigeminal system.[55]

Evidence of ONABOTULINUMTOXINA FOR TREATMENT OF Chronic Migraine

OnaboulinumtoxinA has been reported to relieve pain associated with a variety of conditions, including migraine headache. Unlike its function at the neuromuscular junction, the mechanism of action of OnaboulinumtoxinA in nociception and migraine relief is not clear. It is postulated that OnaboulinumtoxinA inhibits the sensitization of peripheral trigeminal sensory fibers which modulates the activity of central trigeminal neurons, and thus indirectly leads to the inhibition of migraine headache [14]. A systematic series of exploratory controlled trials was conducted to assess the efficacy and safety of onabotulinumtoxinA in patients with migraine, chronic daily headache (CDH), and chronic tension-type headache (CTTH). In the two largest migraine exploratory studies, no significant between-group difference was observed in the frequency of headache episodes [15, 16]. In the CTTH study, no significant between-group difference was observed in the number of tension-type headache-free days per month [17]. Efficacy of onabotulinumtoxinA in migraine and CTTH has therefore not been established.

While the efficacy of onabotulinumtoxinA has not been demonstrated, these trials did help to identify a patient population potentially responsive to onabotulinumtoxinA treatment. A subgroup analysis of patients with the highest baseline frequencies of headache days (ie, ≥12 and ≤15 per month) found that onabotulinumtoxinA-treated patients experienced a significant mean decrease from baseline in headache episodes at Day 180 (the primary timepoint) compared with placebo-treated patients (P=.048).[27] These results suggested that patients suffering very frequent headache attacks may be the ones most likely to benefit from prophylactic onabotulinumtoxinA treatment.

In addition, the results of 2 additional exploratory, well-designed, randomized, double-blind, placebo-controlled trials have provided further insight as to which patients, dosages, and injection protocol may yield the best results from prophylactic onabotulinumtoxinA therapy.[10, 26] Together, these trials recruited >1000 patients with CDH (>15 headache days per month) who could have had any combination of migraines and/or episodic or chronic tension-type headache. Baseline data from these studies indicated that the majority of patients enrolled likely suffered from CM.[10, 26, 41] Each study used a different approach (fixed-site or follow-the-pain, discussed below) and different doses of onabotulinumtoxinA (75 U to 260 U). The primary outcome measures of these exploratory trials were not met, although improvements from baseline for the treatment groups were reported in both trials.[10, 26] In one trial, several secondary measures showed statistically significant benefit with onabotulinumtoxinA treatment versus placebo treatment.[10] In the other trial, a subgroup analysis that excluded patients taking other headache prophylactic treatments, showed a statistically significant improvement in the frequency of headache-free days at 6 months, the

primary endpoint (10.0 days in the onabotulinumtoxinA group vs. 6.7 days in the placebo group, *P*=.038). A significant reduction at 6 months in the mean frequency of headaches per 30 days that favored onabotulinumtoxinA treatment was also observed (-7.8 in the onabotulinumtoxinA group vs. -4.5 in the placebo group; *P*=.032).[41] This subgroup analysis was conducted based on evidence of a statistically significant subgroup interaction, as well as recommendations from migraine controlled-trial guidelines that recommend monotherapy studies since concomitant treatment may confound study results.[42-44] These exploratory phase 2 studies provided guidance and shaped the study design of the phase 3 PREEMPT clinical program.

Another controlled study demonstrated the effectiveness of 100 U onabotulinumtoxinA in the treatment of patients with CM who did not overuse pain medication. Using a fixed-site administration approach, patients in the onabotulinumtoxinA treatment group had a statistically significant and clinically meaningful (31.0%) decrease in migraine frequency (primary endpoint) compared with the 8.9% decline for those in the placebo-treated group (*P*<.001).[11]

More recently, the PREEMPT clinical program confirmed onabotulinumtoxinA as an effective, safe, and well-tolerated prophylactic treatment for adults with CM. Two phase 3, multicenter studies (PREEMPT 1 & 2), each of which had a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase, enrolled 1384 patients with CM. In these studies, all patients received the minimum intramuscular (IM) dose of 155 U of onabotulinumtoxinA administered to 31 injection sites across 7 head and neck muscles using a fixed-site, fixed-dose injection paradigm (each injection was 5 U in 0.1 mL). In addition, up to 40 U onabotulinumtoxinA, administered IM to 8 additional injection sites across 3 head and neck muscles, was allowed, using a follow-the-pain approach. Thus, the minimum dose was 155 U and the maximum dose was 195 U.[29]

Important endpoints (primary and secondary) were change from 28-day baseline compared with the 28 days ending at Week 24 for frequency of headache days (primary PREEMPT 2; secondary PREEMPT 1) and headache episodes (primary PREEMPT 1; secondary PREEMPT 2). Statistically significant reductions from baseline for frequency of headache days after onabotulinumtoxinA treatment compared with placebo treatment in both PREEMPT 1 & 2 (*P*=.006; *P*<.001) were observed [30, 31]. Statistically significant improvement from baseline after onabotulinumtoxinA compared with placebo treatment was seen for headache episodes in PREEMPT 2 (*P*=.003),[31] but not in PREEMPT 1.[30] Pooled analysis demonstrated that onabotulinumtoxinA treatment significantly reduced mean frequency of headache days (–8.4 onabotulinumtoxinA, –6.6 placebo; *P*<.001) and headache episodes (5.2 onabotulinumtoxinA, –4.9 placebo; *P*=.009).[29] Several other efficacy variables (migraine episodes, migraine days, moderate or severe headache days, cumulative hours of headache on headache days, and proportion of patients with severe disability) showed significant between-group differences favoring onabotulinumtoxinA. The PREEMPT results showed highly significant improvements in multiple headache symptom measures and demonstrated improvement in patients' functioning, vitality, psychological distress, and overall quality of life.[29]

Of the total 1384 PREEMPT subjects, 670 (331 onabotulinumtoxinA vs. 339 placebo) received fixed-site and fixed dose (FSFD) injections only during the DBPC phase. The PREEMPT FSFD dose injection paradigm demonstrated that onabotulinumtoxinA significant reduced headache related disability and improved migraine specific quality of life. Pooled analysis also revealed significantly higher 50% and 75% responder rates in subjects receiving onabotulinumtoxinA compared to placebo. The proportion of patients who had a ≥75% reduction from baseline in

headache days at Week 24 (22.8% onabotulinumtoxinA, 15.5% placebo; p=0.002). For all headache symptom measures, a significantly greater proportion of onabotulinumtoxinA-treated than placebo-treated patients had ≥75% decreases from baseline.

A review of randomized, double-blind, placebo-controlled or active-comparator–controlled clinical studies of onabotulinumtoxinA as headache prophylaxis treatment for CM report adverse events (AEs) that were consistent with the known safety and tolerability profile of IM administration of onabotulinumtoxinA. The safety profile indicates that onabotulinumtoxinA is safe and well tolerated in the CM population, with few patients discontinuing treatment due to AEs (1.4% to 3.8%).[10, 29, 45] In contrast, other prophylactic headache treatments report discontinuation rates due to AEs as high as 12.7%.[45] Several epidemiologic surveys indicate that preventive therapies are significantly underutilized; only a minority of patients who could benefit from preventive therapy are currently treated (6% to 13% in population-based surveys).[9, 46, 47] Thus, a substantial proportion of migraine sufferers who might benefit from prevention do not receive it. A study of patient adherence to prophylactic migraine medication showed that 35% of enrolled patients were nonadherent.[48] Another study revealed that approximately 75% of the study population (n=729) had stopped or switched prophylactic treatment for migraine after 1 year.[49] Given the substantial AEs and adherence issues associated with available pharmacotherapies for CM, the relatively mild AEs associated with onabotulinumtoxinA treatment may present an attractive treatment alternative.

THE Injection STRATeGY FOR CHRONIC MIGRAINE

Based on exploratory phase 2 CM studies detailed above,[10, 26] the PREEMPT clinical program has established a successful treatment paradigm.[29-31] This is a standardized paradigm whereby a minimum dose of 155 U of onabotulinumtoxinA is administered as 31 fixed-site, fixed-dose (FSFD) injections across 7 specific head/neck muscles. Up to 40 U of additional onabotulinumtoxinA can be administered at the physician's discretion using a follow-the-pain (FTP) strategy into the temporalis, occipitalis, and/or trapezius muscles, with a maximum dose of 195 U administered to 39 sites. When deciding on dose and location of additional onabotulinumtoxinA, physicians should take into consideration the location of the patient's predominant pain and the severity of palpable muscle tenderness.

The PREEMPT injection paradigm involves a minimum of 31 injections to 7 specific head and neck muscle areas. Patients are placed supine for injections into the corrugator, procerus, frontalis, and temporalis, and these muscles are injected first, in this order. Patients are sitting for injections into the occipitalis, cervical paraspinal, and trapezius muscles. The physician palpates each muscle (bilaterally, if appropriate) prior to injection to verify muscle delineation, and to determine whether there is any muscle tenderness and areas of pain that require additional treatment. The PREEMPT injection paradigm dose for chronic migraine is 155 U to 195 U administered IM using a sterile 30-gauge, 0.5 inch needle (with a Luer Lock) as 0.1 mL (5 U) injections per each site. A 1-inch needle may be needed in the neck region for patients with thick neck muscles. This treatment paradigm recommends gloves be worn while administering the treatment. And, prior to injection, the skin should be cleansed according to standard practice for IM injections (eg, with alcohol). The needle is to be inserted into the muscle with the bevel up, at approximately a 45-degree angle. Once the needle is inserted into the muscle, the hub of the needle is held with one hand to ensure that the needle does not torque in the skin. The plunger is pulled back slightly with the other hand to

ensure no blood return, and the plunger is then pushed to administer 0.1 mL (5 U) to each designated injection site. Injections should not be given intravenously.

Corrugator and Procerus

Injections are begun in the glabellar region, which consists of the corrugator and procerus muscles. These muscles are shallow, so the needle should be kept superficial to avoid hitting the periosteum. A total of 2 FSFD injections will be given to the corrugator muscle, one on each side of the forehead. The injection site is located approximately 1.5 cm (1 finger breadth) above the medial superior edge of the orbital ridge (bony landmark). The thumb is placed under the corrugator muscle and the injection is done with the needle angled up and away from the eye (towards the forehead), to prevent ptosis of the eyelid (Figure 1A). Ptosis occurs when toxin diffuses into the medial portion of the upper eyelid where the levator palpebrae superioris muscle is located.[54]

The procerus muscle will have 1 FSFD injection site, which is midline on the forehead approximately 1.5 cm above and midline to the medial superior aspect of the orbital ridge (bony landmark) of each eye. This injection site is midway between the 2 corrugator injections (Figure 1B). A helpful hint for proper injection placement is to visualize a single horizontal line connecting all 3 of these injections.

Frontalis

The physician then injects the frontalis muscle, which is shallow, so the needle is kept superficial to avoid hitting the periosteum. Each injection will diffuse over an area about 2 cm in diameter once the needle pierces the skin (Figure 1C), thus the needle does not need to be directed upward for these injections. There will be a total of 4 FSFD injections (2 on the left side and 2 on the right). For medial injection sites, visually draw a line up from the medial edge of the eyebrow about 1.5 cm (a finger breadth) from the corrugator injection site. The lateral injection sites are parallel and approximately 1.5 cm lateral of the medial injections sites.

Temporalis

The temporal area receives a total of 8 FSFD injections, 4 to each side. Up to 2 additional injections using the optional FTP paradigm are optional. Prior to any injection, the muscles on both sides of the head are palpated for tenderness or pain. It is suggested that the physician start with the 4 fixed-site injections on the left side of the head as indicated in Figure 1D. Having the patient clench his or her teeth assists in locating the anterior aspect of the temporalis muscle, which can then be palpated. The first injection is made just behind this point, trying to stay behind the hairline. The second injection is approximately 0.5 cm superior and 1.5 cm posterior to the first injection in the medial aspect of the muscle. The third injection site is parallel and approximately 1.5 cm posterior to the second injection. The fourth fixed-site injection is 1.5 cm below and perpendicular to the second injection, into the medial aspect of the muscle (Figure 1D). If a decision is made to inject additional onabotulinumtoxinA into the temporalis muscle, it should be injected in this side before proceeding to the right side of the head (Figure 2D). The PREEMPT injection paradigm recommends that an additional injection site is used rather than increasing the volume for any given prior injection site.

Occipitalis

Prior to injecting the occipital area, both the left and right sides are palpated to identify the areas of tenderness and/or pain. To locate the occipitalis injection sites, the external occipital

protuberance is palpated. The sites will be superior to the supranuchal ridge on either side of this protuberance (Figure 1E). Three injections are administered to the right and left occipitalis muscles, for a total of 6 FSFD injections (Figure 1E). The first injection is given just above the occipital protuberance along the supranuchal ridge and approximately 1 cm left/right (depending on the side) of the external occipital protuberance. The second injection is given approximately 1 cm to the left/right and approximately 1 cm above the first injection. The third injection is given 1 cm medial and 1 cm above the first injection site. According to the FTP optional dosing paradigm, an additional 2 injections can be distributed between the right and left occipitalis muscles (1 injection on each side or 2 injections on 1 side) in the areas identified as having maximal tenderness (Figure 2E).

Paraspinal Muscle Group

Beginning on the left side, the cervical paraspinal muscle group injection sites can be located by palpating the cervical spine (Figure 1F). It is important not to go too deep into the cervical paraspinal and trapezius muscles with the injections and the hub of the 0.5 inch needle serves as a relatively accurate "depth" guide. The first injection is administered lateral to the midline, approximately 3-5 centimeters inferior to the occipital protuberance. A second injection is administered on the same side, 1 cm lateral and superior to the first injection (diagonally toward the ear from the first injection). This procedure is repeated symmetrically on the contralateral side, for a total of 4 FSFD injections.

Trapezius

Lastly, the superior portions of the trapezius muscles are palpated to identify areas of tenderness and/or pain. Beginning on the left side, the muscle is visually divided into 3 sections (Figure 1G). The first injection is administered in the lateral aspect of the muscle. The physician then moves medially, to the mid-portion of the trapezius, to administer the second injection. The third injection is administered medially and superiorly within the third section of the muscle. This procedure is repeated symmetrically on the contralateral side for a total of 6 FSFD injections. According to the FTP optional dosing paradigm, an additional 4 injections can be distributed between the right and left trapezius muscles in the areas identified as having maximal tenderness(Figure 2G). The infero-medial portions of the trapezius muscle (Figure 2G; see arrow) should be avoided to limit the possibility of neck weakness.

Patients are observed for 10-15 minutes following treatment. Patient are advised not to rub or massage the affected areas for 24 hours, and told that any bumps appearing on the forehead should disappear within approximately 2 hours. Patients are advised that they may need, and should use, their acute medications for breakthrough headaches. Retreatment is recommended at 12-week intervals. In the interim, patients are encouraged to maintain a headache diary.

Trigeminal Neuralgia

There is emerging, preliminary evidence that onabotulinumtoxinA may be effective for trigeminal neuralgia. In a randomized, double-blind, placebo-controlled study, 42 subjects with trigeminal neuralgia were randomized to either intradermal/submucosal injections of onabotulinumtoxinA (75units) or saline in the skin area where pain was experienced.[56] Primary endpoints included a reduction in pain severity as assessed by the VAS and pain attack frequency per day. Significant reductions in pain intensity and frequency were seen in the active group and significantly more

responders (>50% reduction in mean painj score at week 12 after injection) were present in the active (68%) compared to the placebo group (15 %). These preliminary findings will need to be confirmed by larger randomized controlled trials.

Frequent Headache Associated with Medication Overuse

The frequent intake of analgesics and other acute headache medications may lead to the development of a secondary headache disorder classified as medication overuse headache (MOH). Most CM patients seeking treatment in tertiary headache clinics overuse acute headache medications.[57] One study found that as many as 73% of CM patients overuse acute headache medications, including simple and combination analgesics, triptans, and opioids.[58] The role of acute medication overuse in CM remains unclear, but it is likely to reflect a more aggressive disease biology, as well as contribute to the transformation from episodic to CM. Although not always successful, and although there are no randomized, placebo-controlled trials demonstrating the effectiveness of drug withdrawal alone, termination of acute headache medication overuse is recommended. However, cessation of acute medications is often not a pragmatic treatment solution for many patients, and preventive medication in addition to rescue therapy is necessary to ensure compliance and successful outcomes.

In the absence of evidence, textbooks and treatment guidelines have suggested that preventive migraine medications will have limited or no effectiveness in the presence of medication overuse (MO). In a planned secondary analysis from two similarly designed, randomized, placebo-controlled, parallel, phase III trials, patients were randomized to treatment groups (155–195 U of onabotulinumtoxinA or placebo) using MO (patient reported and diary-captured frequency of intake) as a stratifying variable. Of 1384 patients, 65.3%(n=904) met MO criteria (onabotulinumtoxinA: n=445, placebo: n=459). For CM+MO subgroup at Week 24, statistically significant between-treatment group mean changes frombaseline favoring onabotulinumtoxinA versus placebo were observed for headache days (primaryendpoint:-8.2 vs. -6.2; $p< 0.001$) and other secondary endpoints: frequencies of migraine days($p<0.001$), moderate/severe headache days ($p<0.001$), cumulative headache hours on headachedays ($p<0.001$), headache episodes ($p=0.028$), and migraine episodes ($p=0.018$) and the percentage of patients with severe Headache Impact Test-6 category ($p<0.001$). At Week 24, change from baseline in frequency of acute headache medication intakes (secondary endpoint) was not statistically significant ($p=0.210$) between groups, except for triptan intakes ($p<0.001$), where onabotulinumtoxinA-treated group was favored. OnabotulinumtoxinA was effective and well tolerated as headache prophylaxis in CM +MO patients

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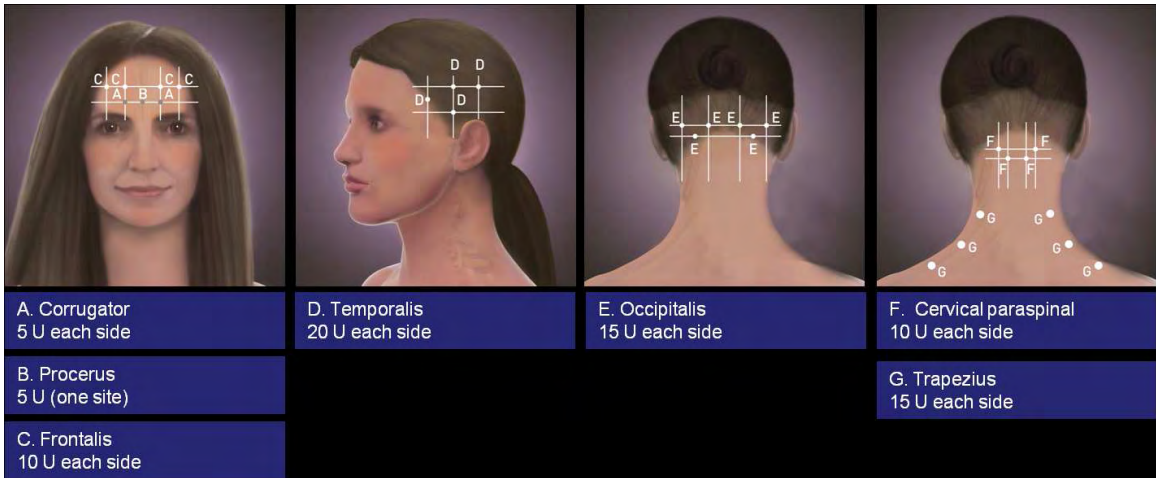

Figure 1: Fixed-site, fixed-dose injection site locations: The (A) corrugators, (B) procerus, (C) frontalis, (D) temporalis, (E) occipitalis, (F) cervical paraspinal, and (G) trapezius muscle injection sites.

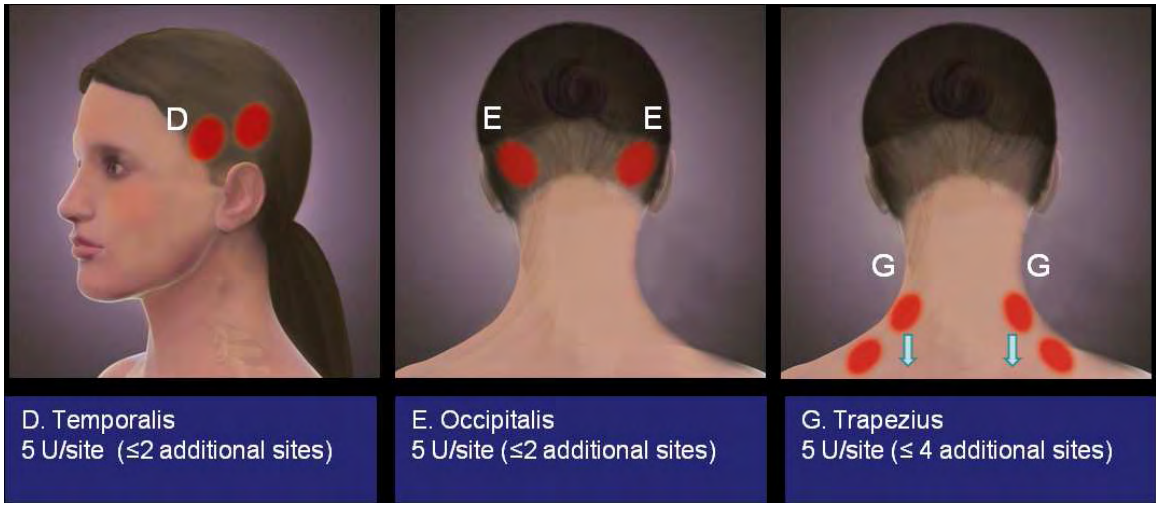

Figure 2: Follow-the-pain muscle areas: Optional injections are distributed between the right and left (D) temporalis, (E) occipitalis, and (G) trapezius muscles in areas of maximal tenderness and/or pain.

Brief Biography

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David W. Dodick, MD, FRCP (C), FACP, is Professor of Neurology at the Mayo Clinic College of Medicine and a consultant in neurology at the Mayo Clinic, in Scottsdale, Arizona. He is the Program Director of the Mayo Clinic Neurology Residency Program and Headache Medicine Fellowship Program. He is the Medical Director of the Headache Program as well as the Concussion Program at Mayo Clinic in Arizona

Dr Dodick received a medical degree with distinction from Dalhousie University, in Halifax, Nova Scotia. He completed an internship and a neurology residency at the Mayo Clinic, in Rochester, Minnesota, followed by fellowship training at the University of Toronto, in Ontario. Dr Dodick is board certified by the Royal College of Physicians and Surgeons of Canada and the American Board of Psychiatry and Neurology (ABPN). He also holds United Council for Neurologic Subspecialties certification in headache medicine and ABPN certification in vascular neurology.

Dr Dodick has authored more than 280 peer-reviewed publications and coauthored 8 books. He serves as Editor in Chief of *Cephalalgia* and is on the editorial board of several journals including The Neurologist, Postgraduate Medicine and Lancet Neurology. He is the Immediate Past-President of the American Headache Society, Chair of the American Migraine Foundation, and Vice-Chair of the World Federation of Neurology Headache Research Group.