Botulinum A toxin injection for chronic migraine

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Objectives

- Role of botulinum toxin A in treatment of chronic migraine
- Proposed mechanism of botulinum toxin A in treatment of chronic migraine
- Adverse effects, warnings and considerations of botulinum toxin A injection for chronic migraine
- Protocol and landmarks of injection for chronic migraine
- Overview of EFNS guideline recommendations for botulinum toxin A injection for chronic migraine

What is chronic migraine?

- OnabotulinumtoxinA is recommended for treatment of patients with CM and considered an effective and well tolerated treatment.
- Chronic migraine (CM) is a debilitating disorder affecting approximately 2% of the general population

ICHD-3 criteria for migraine and chronic migraine

(A) Migraine-like or tension-type- like headache on ≥15 days/month for >3 months that fulfill criteria B and C

(B) Occurring in a patient who has had at least five attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura

(C) On ≥8 days/month for >3 months, fulfilling any of the following:

1. Criteria C and D for migraine without aura
2. Criteria B and C for migraine with aura
3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

(D) Not better accounted for by another diagnosis

ONABOTULINUM TOXIN A

- Possible efficacy of onabotulinumtoxinA in migraine was incidentally noted in patients treated cosmetically for wrinkles.
- In 2010, onabotulinumtoxinA was reported effective for the treatment of CM in the Phase 3 PREEMPT trials and was approved both by the EMA and FDA for the prophylaxis of CM.
- OnabotulinumtoxinA has not been found effective in episodic migraine or in tension-type headache.

Postulated mode of action in Chronic migraine

antagonizes peripheral and central sensitization and nociceptive activation of the trigeminovascular pathway

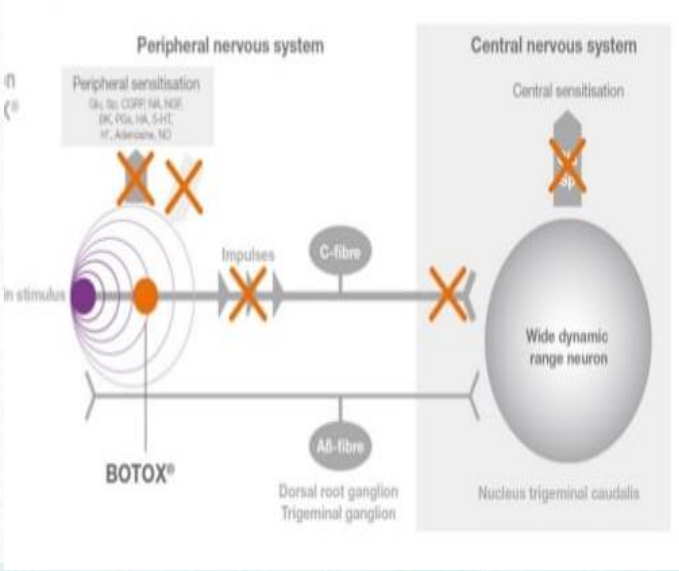
- inhibit release of neurotransmitter(CGRP, glutamate,substance P)

➢Inhibit neurogenic inflammation

- Inhibit afferent neuronal-firing and pain conducting nerve fibers

➢Reduce pain signal conduction to CNS

- Enhancement of opioidergic transmission



The most frequent adverse reactions following injection of botulinum toxin for chronic migraine

- neck pain (9% vs 3%)
- headache (5% vs 3%)
- eyelid ptosis (4% vs < 1%)
- migraine (4% vs 3%)
- muscular weakness (4% vs < 1%)
- musculoskeletal stiffness (4% vs 1%)
- bronchitis (3% vs 2%)
- injection-site pain (3% vs 2%)
- musculoskeletal pain (3% vs 1%)
- myalgia (3% vs 1%)
- facial paresis (2% vs 0%)
- hypertension (2% vs 1%)
- muscle spasms (2% vs 1%)

Most reported side-effects are mild or moderate, transient and self limiting, with very few serious AEs.
Incidence of adverse events decreases with treatment duration.

Spread of toxin effects.

In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism.

- Asthenia, generalized muscle weakness
- Diplopia, ptosis
- Dysphagia, dysphonia, dysarthria
- Urinary incontinence
- Breathing difficulties

These symptoms can happen hours, days, to weeks after receiving an injection of botulinum toxin particularly in unapproved indications and in those who have underlying condition.

Hypersensitivity Reactions

- Serious and/or immediate hypersensitivity reactions have been reported.
- These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea.
- If such a reaction occurs, further injection of botulinum toxin should be discontinued and appropriate medical therapy immediately instituted.

DRUG INTERACTIONS

- Co-administration of botulinum toxin and aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.
- Use of anticholinergic drugs after administration of botulinum toxin may potentiate systemic anticholinergic effects.
- Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of botulinum toxin.
- Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

CONTRAINDICATIONS

- Botulinum toxin is contraindicated in:

  The presence of infection at the proposed injection site(s)

  Hypersensitivity to any botulinum toxin preparation

Warnings and Precautions

- Increased Risk of Clinically Significant Effects should be monitored when given botulinum toxin to:

  - Pre-Existing Neuromuscular Disorders
  - Individuals with peripheral motor neuropathic diseases
  - Amyotrophic lateral sclerosis
  - Neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome)

Use In Specific Populations

- ✓ Safety in pregnancy

  Limited available data indicates onabotA demonstrates no adverse outcomes in pregnancy.

- ✓ Lactation:

  No data are available on onabotA safety during lactation.

- ✓ Pediatric Use:

  Limited available data supports the use of botulinum type A for chronic migraines in pediatric patients (11-18 yr.)

General injection considerations

- ✓ A sterile 30-gauge, 0.5-inch needle should be used.
- ✓ A 1-inch needle may be used in neck regions for patients with thick muscles.
- ✓ Standard sterile procedures for intramuscular injection should be used (eg, swabbing each injection site with alcohol).
- ✓ For each injection, the injection volume will be 0.1 mL (equivalent to 5 Units botox, 15-20 Unit Dysport)

General injection considerations

- Evaluate the anatomy, including relevant function and the effects of treatment on these muscles (eg, weakening)
- Recognize unique anatomy, as no 2 patients are alike; focus on the muscle, not measurements, to adjust for individual anatomical variations
- Consider location, depth, and angle carefully, as the site of medication delivery may be different from the needle insertion point

General injection considerations

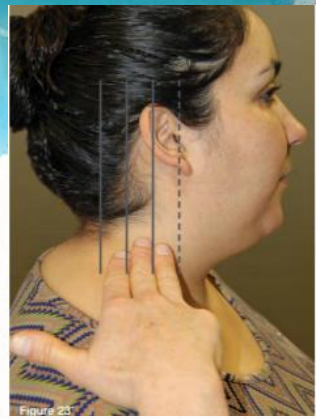
BEFORE INJECTION

- Examine the patient to identify unique anatomy and any muscle weakness or pain/tenderness
  - Visually inspect the muscle
  - Ask the patient to activate the muscle
  - Palpate the muscle
- Verify the needle is securely fastened to the injection syringe
- Line up the bevel of the needle with the gradations on the syringe so the bevel is facing upward(this will help you more easily orient the bevel of the needle when injecting)

Pre-examination; What to look for:

- Brow ptosis, possibly compensated by active frontalis muscles, of which the patient may be unaware.
- How to examine: Ask the patient to activate the frontalis muscle by raising and lowering her eyebrows.
- Observe the dynamic muscle activity and whether there is any compensatory mechanism keeping the eyelids open in the presence of brow weakness.

Pre-examination; What to look for:



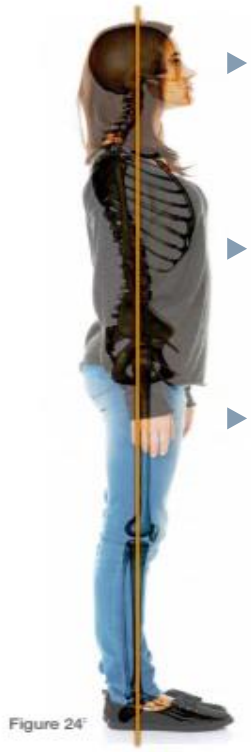


Figure 24

- Neck pain and neck weakness may be present among Chronic Migraine patients.
- Inspect the patient for a head-forward position, which may indicate preexisting muscle weakness.
- How to examine: Observe the patient, standing, with a neutral-spine position. Look for a vertical line from the tragus and anterior ridge of the trapezius through the patient's center of gravity. If the tragus is anterior to this line by 2 to 3 fingerbreadths, this may be abnormal

DURING INJECTION

Inject on 1 side first for bilateral injections then proceed to the other side and repeat at all the specified sites

Consider changing needles frequently to reduce patient discomfort; consider using 1 needle per area or changing every 4 to 6 sites

Inject with the bevel up, pointing away from the skin

It may be helpful to **hold the hub of the needle with 1 hand** to ensure the needle does not twist – Push the plunger with the other hand to administer the medication

Aspirate to ensure no blood return

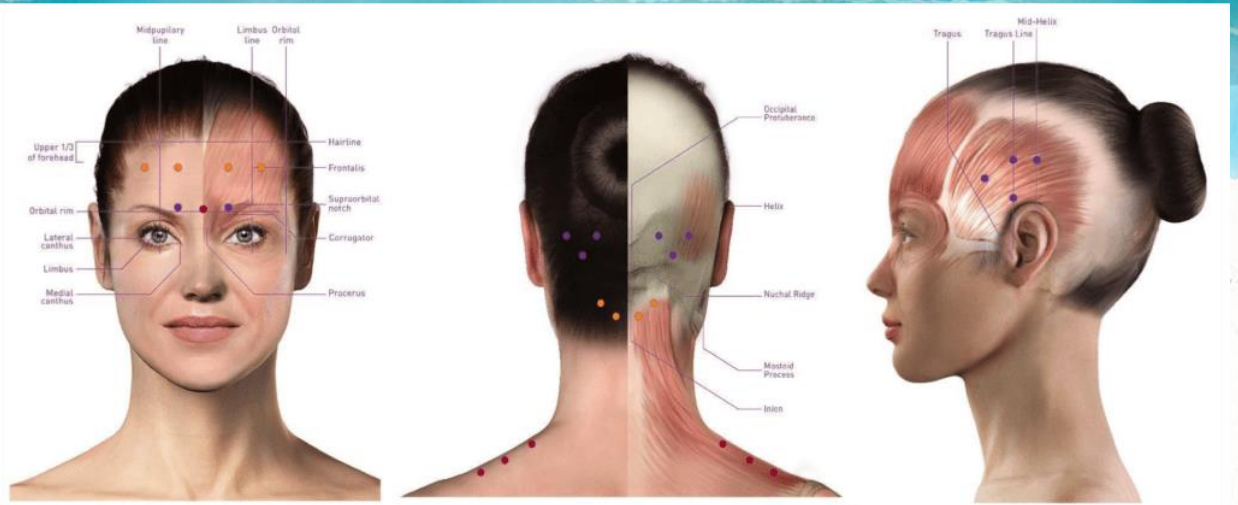
Target the muscle—The needle should be inserted through the epidermis/dermis layer, which may feel more rigid when penetrated. The injection should be given just when there is a decrease in resistance, avoiding the periosteum. This decrease in resistance may be subdermal, not intramuscular.

DURING INJECTION

- An ice pack is used to cool the skin immediately before injections, as it is important to minimize any irritation caused by needles in migraine patients.
- Avoiding bruising or hematoma by keeping distance from vessels.
- Use normal saline (no distil water) as diluent.

Botulinum toxin A injection for Chronic Migraine

- FDA approved for chronic migraine.
- PREEMPT standard protocol: 155 units in 31 site
- Botox,
  - 100 unit vial : 2 mL(Saline): 5 Units per 0.1 mL
  - 200 unit vial: 4 mL(Saline): 5 Units per 0.1 mL
- Dysport
  - 300 unit vial :2.5-3 mL(Saline) : 12.5-10 Units per 0.1 mL
  - 500 unit vial: 2.5-3.1 mL (Saline) : 15-20 Units per 0.1 mL

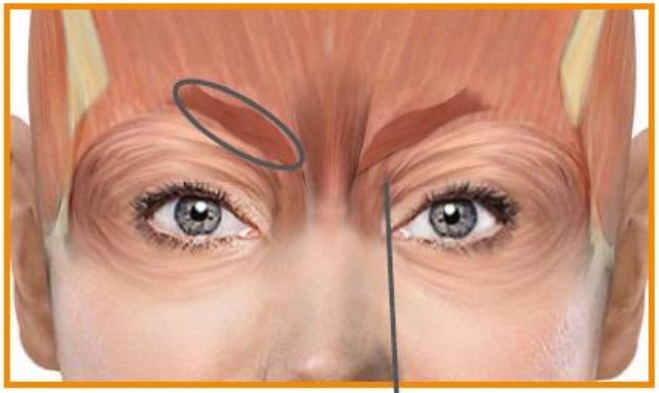


MUSCLE AREA	RECOMMENDED DOSE/NUMBER OF SITES
Corrugator	10 Units divided between 2 sites
Procerus	5 Units in 1 site
Frontalis	20 Units divided between 4 sites
Temporalis	40 Units divided between 8 sites
Occipitalis	30 Units divided between 6 sites
Cervical paraspinal	20 Units divided between 4 sites
Trapezius	30 Units divided between 6 sites
TOTAL DOSE	155 Units† divided between 31 sites

Standard corrugator PREEMPT protocol*

Dose[1]

- 5 Units (0.1 mL) in each site
- Total of 10 Units divided into 2 sites

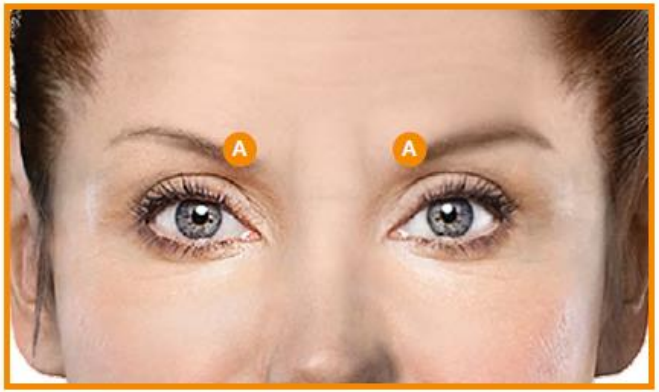


Corrugator muscle[18,*]

Medial inferior edge of the superior orbital rim[18,*]

Injection site A

- About 1.5 cm (≈ 1 fingerbreadth) above the medial inferior edge of the superior orbital rim (bony landmark). This may vary based on individual anatomy



Corrugator injection sites[1]

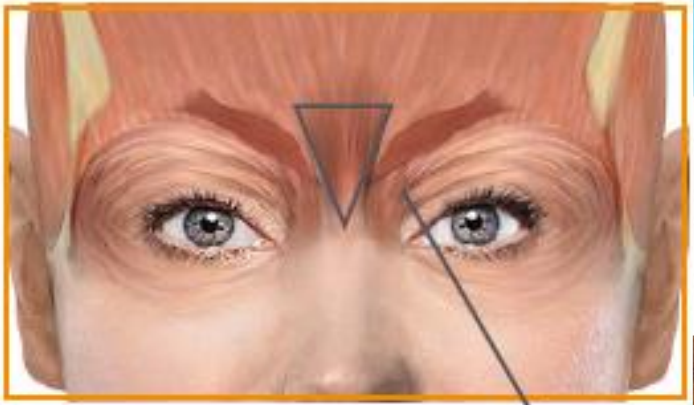
Figure 3

Figure 6

Standard procerus PREEMPT protocol*

Dose†

- 5 Units (0.1 mL) in 1 site
- Total of 5 Units



Procerus muscle[18,*]

Medial inferior edge of the superior orbital rim[18,*]

Figure 4†

Injection site B

- The base of the procerus resides approximately midway between the 2 corrugator injections

Procerus injection site†


Figure 7

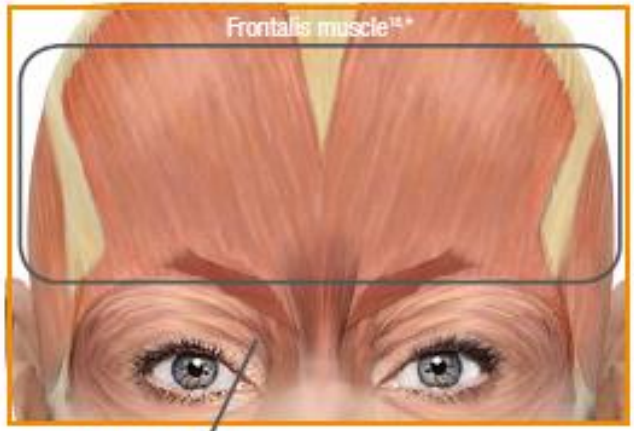
Standard frontalis PREEMPT protocol*

Dose[1]

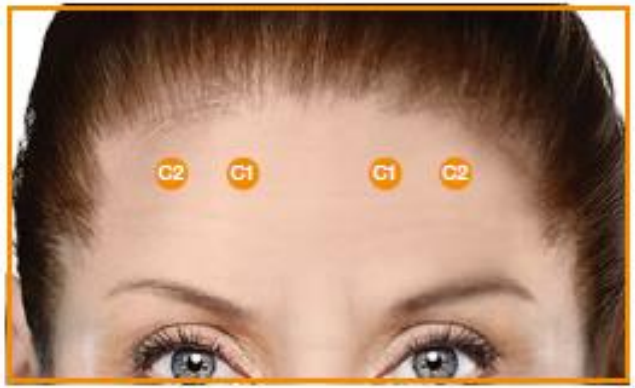
- 5 Units (0.1 mL) in each site
- Total 20 Units divided into 4 sites

Medial injection site C1

- Visually, draw a vertical line up from the medial inferior edge of the superior orbital rim
- Medial injection is generally within the upper one-third of the forehead, and at least 1.5 cm (≈ 1 fingerbreadth) above the corrugator injection site. This may vary based on individual anatomy



Medial inferior edge of the superior orbital rim[16,*]



Frontalis injection sites[1]

Lateral limbus of the cornea[16,*]

Lateral injection site C2

- Lateral injections are parallel, lining up with the lateral limbus of the cornea, and at least 1.5 cm (≈ 1 fingerbreadth) lateral to the medial injection site (Figure 8). This may vary based on individual anatomy

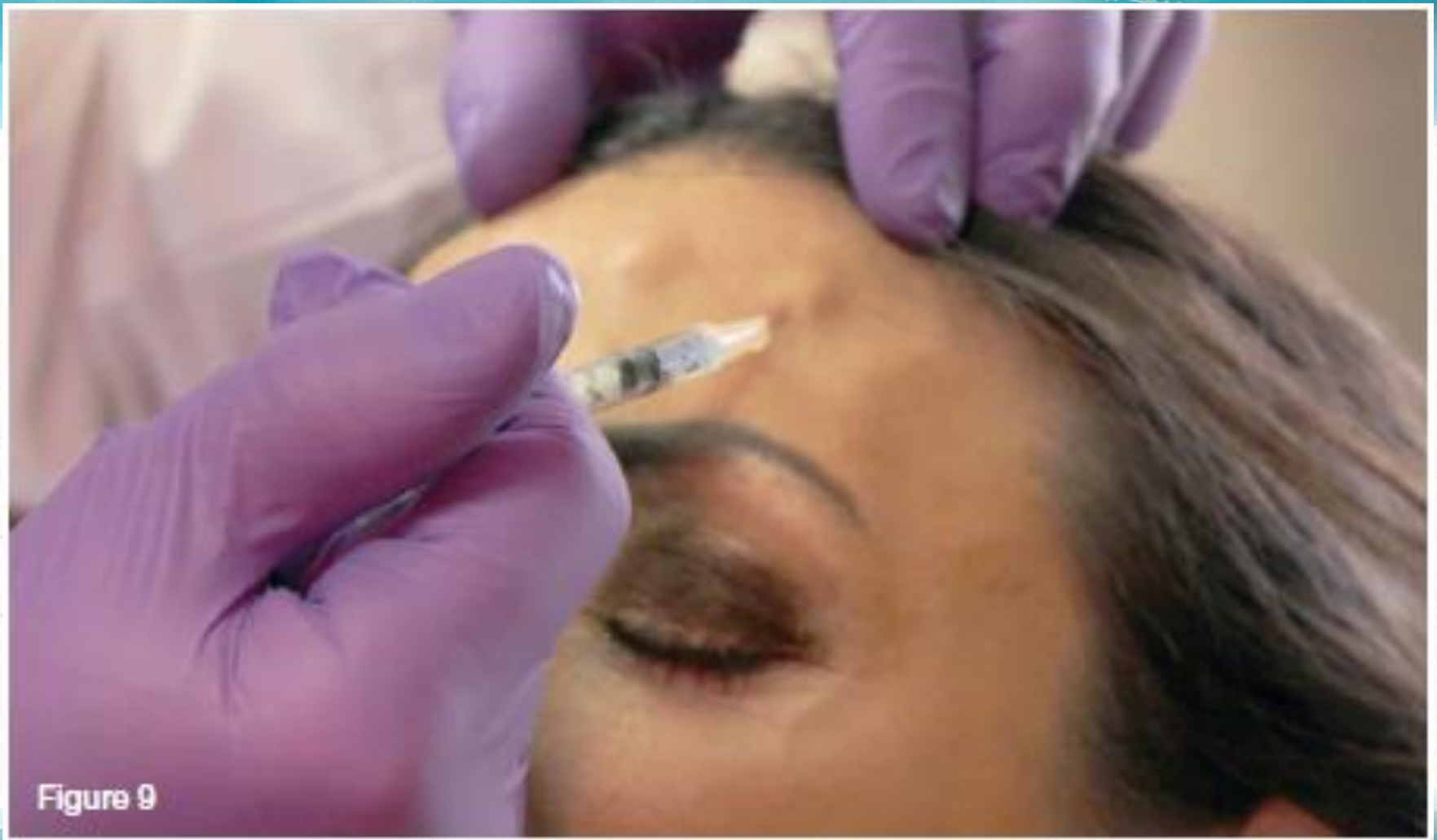


Figure 9

Standard temporalis PREEMPT protocol*

Dose[1]

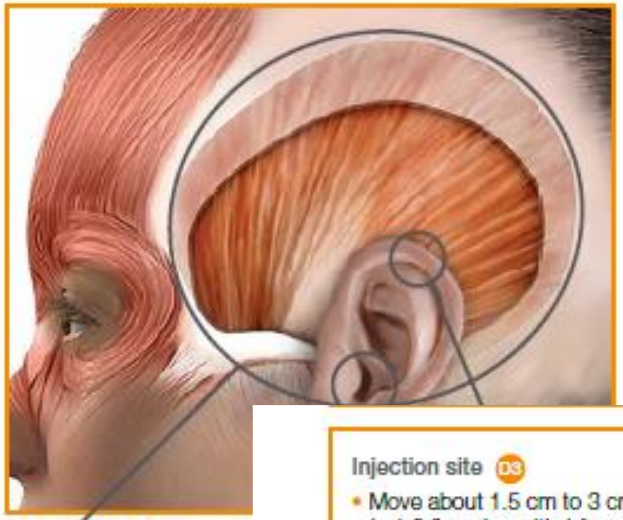
- 5 Units (0.1 mL) in each site
- Total 40 Units divided into 8 sites (4 on each side of head)

Injection site D1

- Find the tragus of the ear and move your finger vertically up the side of the head about 3 cm (≈ 2 fingerbreadths)

Injection site D2

- Move about 1.5 cm to 3 cm (≈ 1-2 fingerbreadths) up from the first injection, still in line with the tragus of the ear



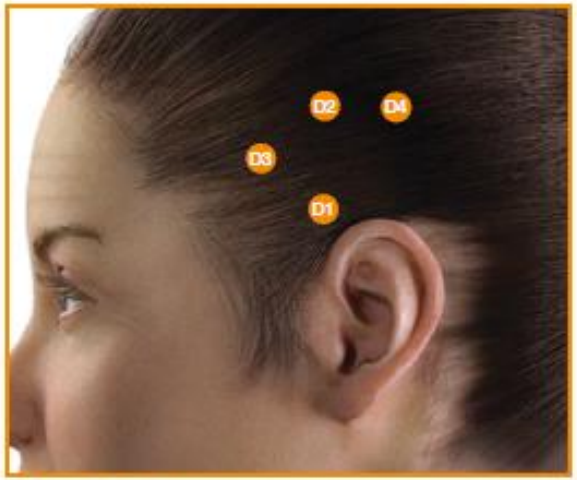
Temporalis muscle[18,*] T

Injection site D3

- Move about 1.5 cm to 3 cm (≈ 1-2 fingerbreadths) forward, toward the face, from the first and second injections. Make the third injection halfway vertically between injection sites 1 and 2

Injection site D4

- Move about 1.5 cm (≈ 1 fingerbreadth) back from the second injection, and in line with the midportion (helix) of the ear



Temporalis injection sites[1]

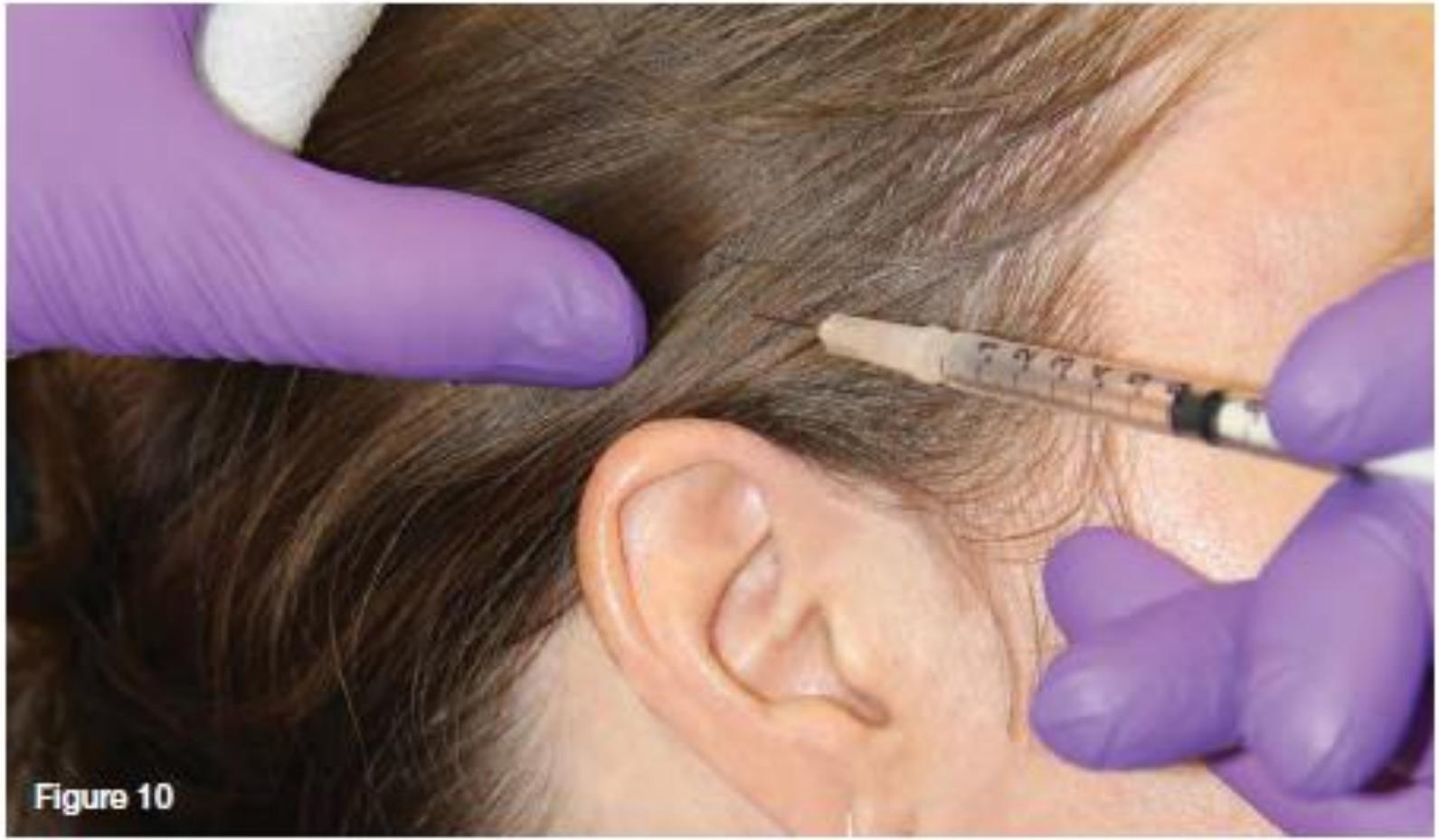


Figure 10

Standard occipitalis PREEMPT protocol*

Dose[1]

- 5 Units (0.1 mL) in each site
- Total 30 Units divided into 6 sites (3 on each side)

Injection site E1

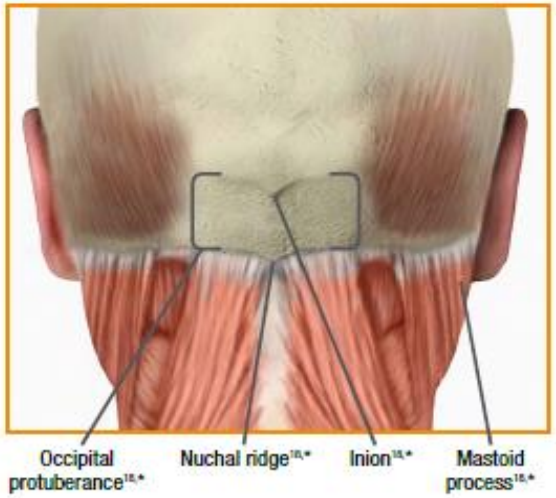
- Palpate the occipital protuberance and find the most posterior point (inion) in the midline (Figure 13, page 25)
- Locate the tip of the mastoid process behind the ear (Figure 13, page 25)
- Place your thumb on the midpoint of the occipital protuberance (inion) and your index finger on tip of the mastoid process
- Divide the space between your thumb and index finger in half
- Place the first injection just above the nuchal ridge at this midpoint

Injection site E2

- Measure a diagonal fingerbreadth up and out toward the superior helix of the ear (see diagram on page 20) for the second muscle area for injection (eg, at the 10 o'clock position for the left injection)

Injection site E3

- Measure a diagonal fingerbreadth up and medial for the third muscle area for injection (eg, at the 2 o'clock position for the left injection)



Occipitalis injection sites[1]

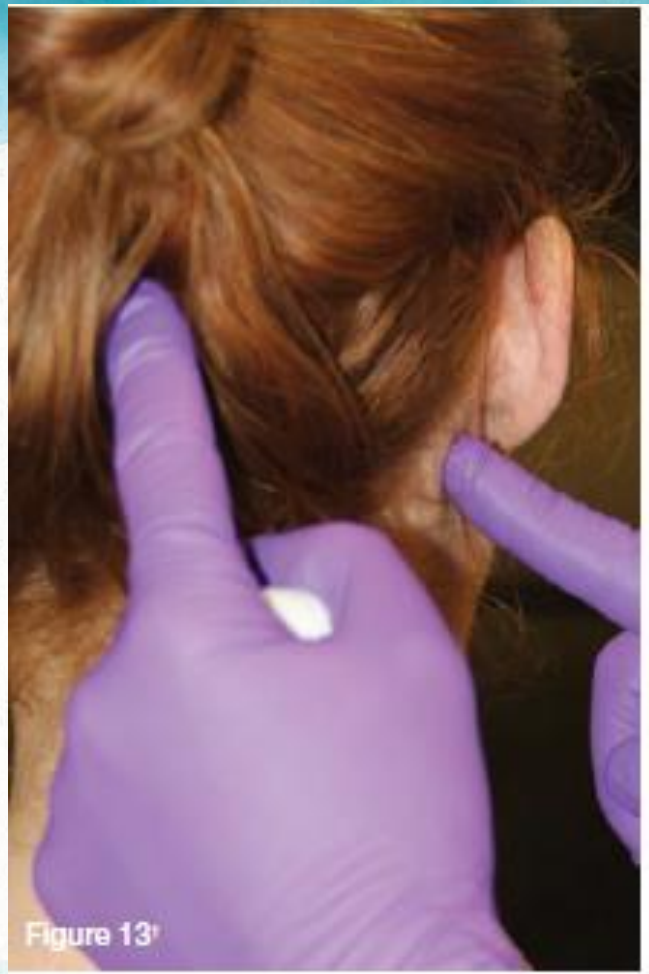


Figure 13

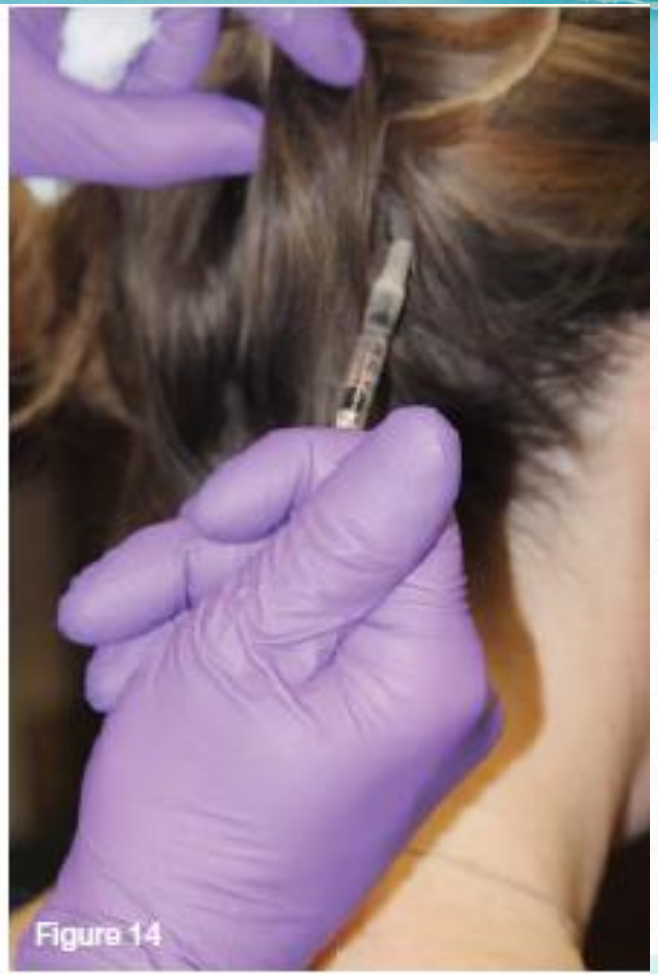


Figure 14

Standard cervical paraspinal PREEMPT protocol*

Dose[1]

- 5 Units (0.1 mL) in each site
- Total 20 Units divided into 4 sites (2 on each side)

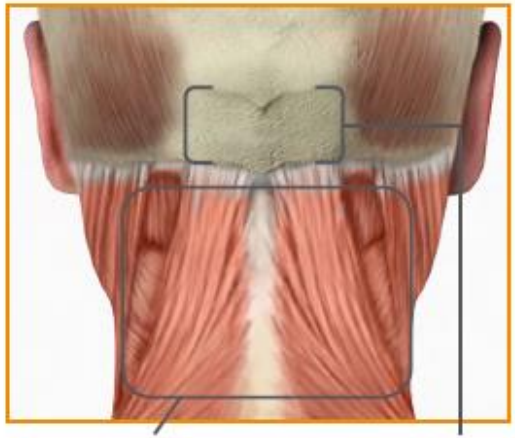
Injection site F1

- Measure about 1 cm left of the midline of the cervical spine and about 3 cm (≈ 2 fingerbreadths) inferior to the lower border of the occipital protuberance

Injection site F2

- Measure about 1.5 cm (≈ 1 fingerbreadth) diagonally up at a 45° angle toward the helix of the ear (see diagram on page 20) from the first injection site

*Muscles and anatomical structures shown for anatomical reference only.



Cervical paraspinal muscle group[15,*] Occipital protuberance[15,*]

Cervical paraspinal injection sites[1]

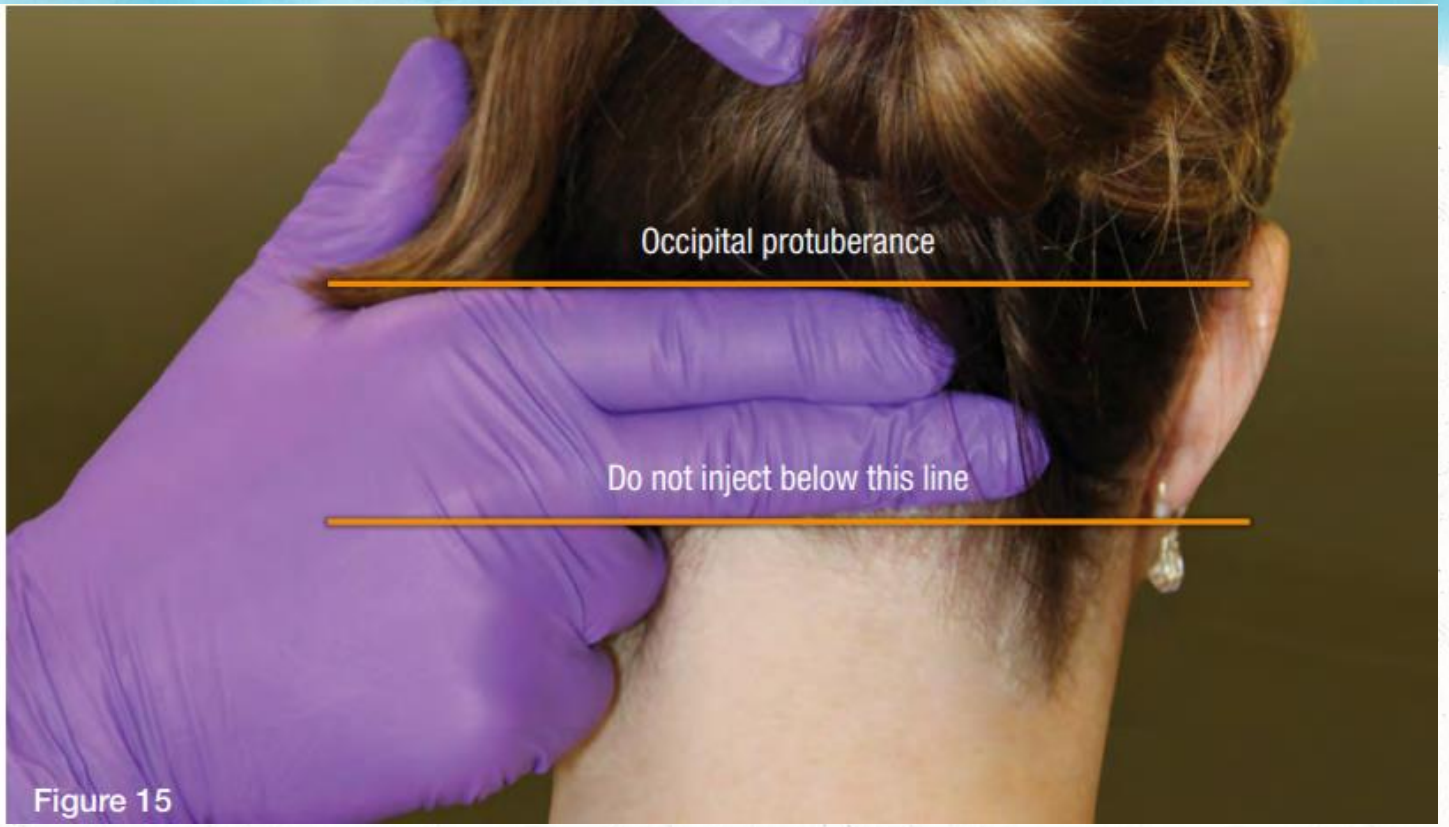


Figure 15

Standard trapezius PREEMPT protocol*

Dose[1]

- 5 Units (0.1 mL) in each site
- Total 30 Units divided into 6 sites (3 on each side)

Injection site G1

- Divide the upper portion of the trapezius muscle in half, from the inflection point of the neck (necklace line) to the acromioclavicular joint
- The first injection is located at this midpoint

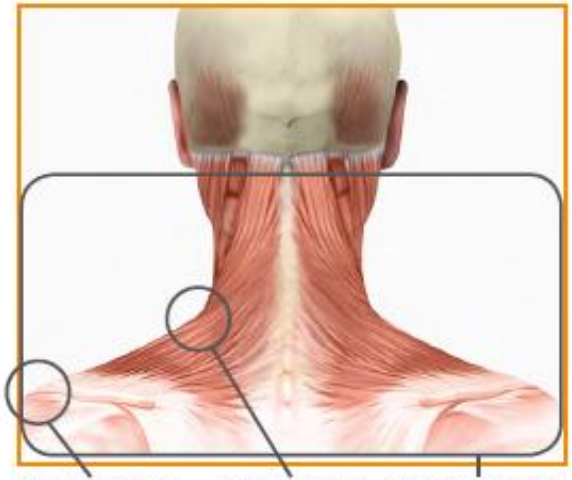
Injection site G2

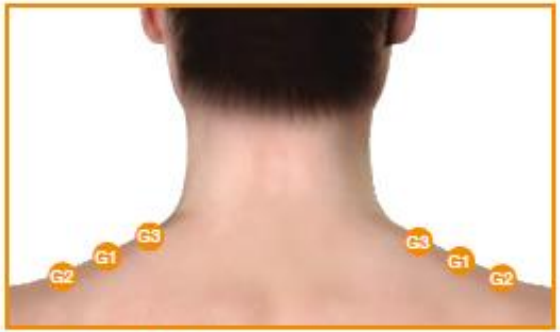
- Split the difference between injection 1 and the acromioclavicular joint

Injection site G3

- Split the difference between injection 1 and the necklace line

*Muscles and anatomical structures shown for anatomical reference only.





Trapezius injection sites[1]

Figure 16

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Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation

Lars Bendtsen[1*], Simona Sacco[2], Messoud Ashina[3], Dimos Mitsikostas[4], Fayyaz Ahmed[5], Patricia Pozo-Rosich[6,A] and Paolo Martelletti[7]

For patients with CM when should onabotulinumtoxinA be offered?

- It is recommended that patients should have failed at least two to three other migraine prophylactics unless contraindicated by comorbid disorders before onabotulinumtoxinA is administered.

Bendtsen et al. The Journal of Headache and Pain (2018) 19:91
https://doi.org/10.1186/s10194-018-0921-8

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For patients with CM plus medication-overuse should withdrawal be done before treatment with onabotulinumtoxinA is initiated?

- In patients with CM and medication overuse, it is preferable to detoxify first with later initiation of onabotulinumtoxinA.
- If this is not feasible, onabotulinumtoxinA can be initiated from the start or even before withdrawal of the overused medication

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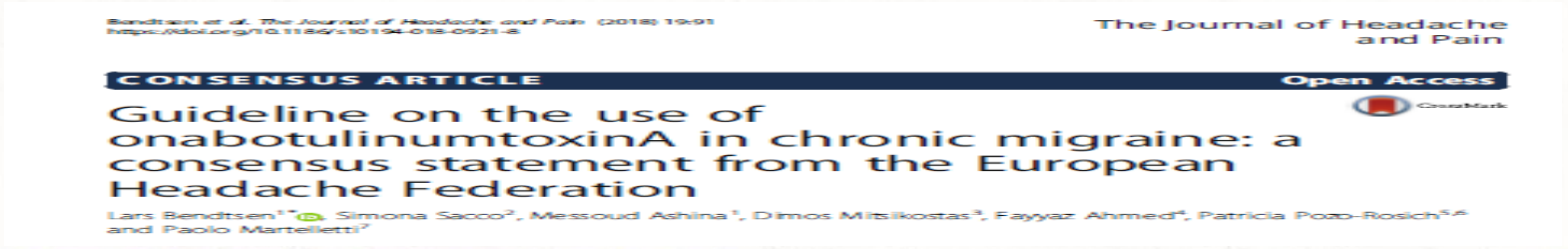
How should treatment with onabotulinumtoxinA be administered?

- The PREEMPT injection protocol (injection of 155 U– 195 U administered to 31–39 sites every 12-weeks) should be followed.
- It is possible that 195 U is more effective than 155 U. The higher dose could be considered, if the patient does not respond to 155 U.



When can a patient be considered non-responder to onabotulinumtoxinA?

- It is recommended that patients should be defined as non-responders, if they have less than 30% reduction in headache days per month during treatment with onabotulinumtoxinA.
- However, other factors such as headache intensity, disability and patient preferences should also be considered.
- Treatment should be stopped, if the patient does not respond to the first 2–3 treatment cycles.

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- We recommend to stop treatment in patients with a reduction to less than 10 headache days per month for 3 months. However, other factors such as headache intensity, disability and patient preferences should also be considered.
- Patients should be re-evaluated 4–5 months after stopping onabotulinumtoxinA to make sure that the patient has not returned to CM.

Thank you for your attention