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# Botulinum Toxin In The Management Of Migraine

**A Project Submitted to**

**The College of Dentistry, University of Baghdad, Department of Oral medicine in Partial Fulfillment for the Bachelor of Dental Surgery**

**By**

**Somaia Ahmed Abed Alamer**

**Supervised by**

**Assistant Lecturer Dr. Noor Saad M. Ali B.D.S, (M.Sc. (Oral Medicine)**

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# Dedication

I dedicate this project to my parent, my sisters and my friends, my source of unlimited support & who always encourage me to do the best.

Also I would like to express appreciation for my supervisor Dr. Noor Saad for her precious efforts to help me.

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## Abstract

Botulinum toxin type A, a neurotoxin, is effective for treating a variety of disorders of involuntary muscle contraction including cervical dystonia, blepharospasm, and hemifacial spasm. It inhibits neuromuscular signaling by blocking the release of acetylcholine at the neuromuscular junction. The biological effects of the toxin are transient, with normal neuronal signaling returning within approximately 3 to 6 months postinjection.

Recent clinical findings suggest that botulinum toxin type A may inhibit pain associated with migraine and other types of headache.. Research findings suggest that botulinum toxin type A inhibits the release of neurotransmitters from nociceptive nerve terminals and, in this way, may possess an analgesic effect. A number of retrospective open-label chart reviews and placebo-controlled trials have demonstrated that localized injections of botulinum toxin type A significantly reduce the frequency, severity, and disability associated with migraine headaches. Although the majority of patients in these studies experienced no botulinum toxin type A-mediated side effects, a small percentage of patients did report transient minor side effects including blepharoptosis, diplopia, and injection-site weakness. Currently, 4 randomized, placebo-controlled, clinical trials are being conducted to evaluate the efficacy, optimal dosing, and side-effect profile of botulinum toxin type A as a novel treatment for migraine and other types of headache.

## Introduction

Migraine is a genetically influenced complex disorder characterized by episodes of moderate-to-severe headache felt as a throbbing pain on one side of the head, generally associated with nausea and increased

sensitivity to light and sound. Migraine attacks are a complex brain event that unfolds over hours to days, in a recurrent matter. [1]

Migraine is highly prevalent, affecting 12% of the population, attacking up to 17% of women and 6% of men each year. [2] [3]

Migraine tends to run in families. It is consistently the fourth or fifth most common reason for emergency visits accounting for an annual 3% of all emergency visits.[4] Its prevalence increases in puberty but continues to increase until 35 to 39 years of age, decreasing later in life, especially after menopause. [2]

The causes of migraine aren't really clear, but genetics and environment do play a role. Most people with migraine will have spontaneous attacks, meaning there is nothing they did or didn't do to trigger the attack. Some people will have attacks that have an identifiable cause. Everyone has different triggers**.** [5]

Some symptoms of migraine include Intense throbbing or dull aching pain on one side of your head or both, pain that worsens with physical activity, Nausea or vomiting, blurred vision or blind spots, being bothered by light, noise, or odors, feeling tired and/or confused, Stopped-up nose, feeling cold or sweat, stiff or tender neck, tight headedness, tender scalp. [6]

Migraine treatment involves acute (abortive) and preventive (prophylactic) therapy. Patients with frequent attacks usually require both. Measures directed toward reducing migraine triggers are also generally advisable.

Acute treatment aims to reverse, or at least stop, the progression of a headache that has started. Preventive treatment, which is given even in the absence of a headache, aims to reduce the frequency and severity

of the migraine attack, make acute attacks more responsive to abortive therapy, and perhaps also improve the patient's quality of life. [7]

Botulinum toxin is a protein and neurotoxin produced by the bacterium Clostridium botulinum. It is a selective blocker of acetylcholine release from nerve endings, which blocks neural transmission when injected into muscle. [8]

Botulinum toxins, are used for the treatment of facial rhytides (for example, lateral orbital wrinkles, lower eyelid wrinkles, and labial lines), by producing weakness or paralysis of the associated muscles, and in the treatment of hyperhidrosis. The toxin binds with high affinity to peripheral cholinergic nerve endings, such as those at the neuromuscular junction and in the autonomic nervous system, preventing the release of the neurotransmitter acetylcholine. [9]

Botulinum toxin has been investigated for the treatment of several headache disorders. The beneficial effect of botulinum toxin type A treatment for migraine was first noted in patients who were given the protein for cosmetic purposes treating facial rhytides and reported relief from their migraine headaches [10, 11]. The pooled result of these studies showed that botulinum toxin type A was significantly superior to placebo in reducing headache days and multiple quality-of-life measures [12, 13].

## Aims of the study

To review the history of botulinum toxin in migraine and presents the clinical evidence for the use of botulinum toxin in the treatment of migraine.

# Chapter one

# Review of Literature

## 1.1 Migraine

### 1.1.1 Definition

Migraine is a common, chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurologic symptoms.[14, 15]

The word migraine is derived from the Greek word "hemikrania," which later was converted into Latin as "hemigranea." The French translation of such a term is "migraine."[1] Migraine is a common cause of disability and loss of work. Migraine attacks are a complex brain event that unfolds over hours to days, in a recurrent matter. The most common type of migraine is without aura (75% of cases).

### 1.1.2 Epidemiology

In the years prior to puberty, migraine is more common among males than females. By the onset of puberty, migraine is more prevalent in females, and by the late teens, females are about twice as likely to suffer from migraine as males. The prevalence of migraine peaks in both sexes during the most productive years of adulthood (age 25 to 55 years). [16]

One-year migraine prevalence rates in the general population for Western countries vary from 4% to 9% in men and from 11% to 25% in women. Non-Western countries report lower figures. Incidence rates for people under 30 years of age vary from 1.5 to 6 per 1000 person-years in men and from 3 to 24 per 1000 person-years in women. Data on the

prevalence of migraine in general, on the gender ratio and on the variations in prevalence in the different age ranges are fairly comparable and can be regarded as very close to reality. On the contrary, data on the incidence of migraine, on the prevalence of different migraine subtypes, such as migraine with aura and the so-called migrainous disorder, and on the frequency of migraine attacks show a striking discordance that somewhat undermines their reliability. The main critical points in prevalence and incidence studies are migraine definition and the methodological approaches used for case screening. Even if International Headache Society (IHS) classification is certainly an improvement over previous tools used in epidemiological studies, the diagnostic criteria for migraine without aura are quite scanty and not easily remembered by subjects belonging to the general population, and those for migraine with aura appear not only difficult to translate for use in a questionnaire or an interview, but also too loose. In particular, the lack of any low-end limit for aura duration may cause an overestimation of migraine with aura prevalence. [17]

As regards sociocultural background, classic medical literature reported a higher prevalence of migraine in subjects with a higher level of education. In 1992 reported just the opposite [18], but in 2002 it no longer found any such difference [19]. the prevalence of migraine increased as household income decreased [18], but no such correlation was found in most of the other surveys [20,21,22]. In the medical literature there are so far only four studies on migraine incidence. Of these, two are retrospective studies [23, 24] that have clear limitations inherent in recall of age at migraine onset, such as telescoping, failing to report real symptoms, and incorrectly reporting symptoms not actually experienced. These retrospective studies and another study conducted

through the linked medical record system show incidence rates that are not much different (for people under 30 years of age, about 1.5–2 per 1000 person-years in men, and about 3–6 per 1000 personyears in women). [25]

### 1.1.3 PATHOPHYSIOLOGY

At first, there was a vascular theory of migraine, which explained that the headache was produced by vasodilation and aura by vasoconstriction, but this theory is not viable anymore. [26] Nowadays, the suggestions pose that multiple primary neuronal impairments lead to a series of intracranial and extracranial changes that cause migraines. [27]

The cortical spreading depression of Leão, a propagating wave of neuronal and glial depolarization that initiates a cascade, is hypothesized to cause the aura, activate trigeminal afferents, and alter the hematoencephalic barrier permeability by activating brain matrix metalloproteinases. [28] In migraine without aura, the suggestions are that cortical depression may occur in areas where depolarization is not consciously perceived, such as the cerebellum. [29] There is activation of trigeminal afferents by neuronal pannexin-1 megachannel opening and subsequent activation of Caspase-1, followed by the release of proinflammatory mediators, activation of NF-kB (nuclear factor kappa-B), and spreading of this inflammatory signal to trigeminal nerve fibers around vessels of the pia mater. [30] This causes a series of cortical, meningeal, and brainstem events, provoking inflammation in the pain-sensitive meninges that concludes in headaches through central and peripheral mechanisms. [31][32] This pathway can, therefore, explain the

cortical depression (which establishes the aura) and the latter prolonged activation of trigeminal nociception (which leads to headache).

The anterior structures are most innervated by the ophthalmic division of the trigeminal nerve, which could explain the pain in the anterior region of the head. There is a convergence of fibers from the upper cervical roots, which originate the trigeminal nerve neurons along with the trigeminal ganglion and the trigeminal nerve at the trigeminal nucleus caudalis, which can explain the anterior to the posterior distribution of pain, from where the fibers ascend to the thalamus and the sensory cortex. [33]

Neurogenic inflammation, which is based on vasodilation, edema, and plasma protein extravasation, results from nociceptor activation, in this case, the trigeminal system. It is associated with the release of substance P, calcitonin gene-related peptide, and neurokinin a, all vasoactive neuropeptides liberated by trigeminal ganglion stimulation. [34] Elevated levels of these neuropeptides have been found in the spinal fluid of chronic migraine patients. [35][36] Neurogenic inflammation can lead to sensitization, which is the process in which neurons tend to become more responsive to stimulation. This can explain some clinical symptoms of the pain and the conversion from episodic migraine to chronic one.[37]

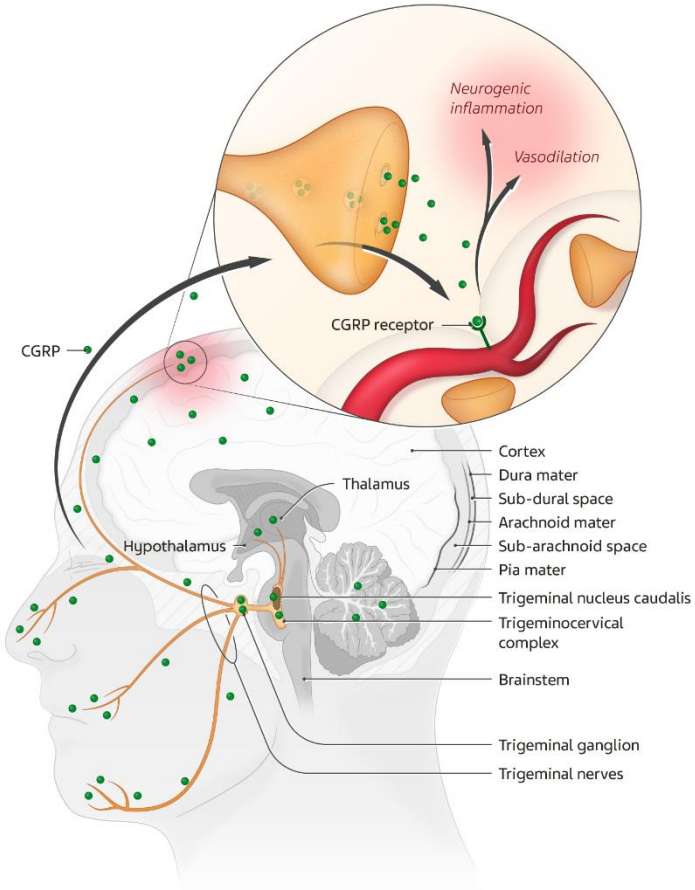


**Figure 1.1** The anatomy of the migraine brain[41,42]

Serotonin, released from the brainstem serotonergic nuclei, may play a role in migraine; however, the exact role of its mechanisms remains a matter of controversy. Most likely, serotonin levels are low between attacks because it may cause a deficiency in the serotonin pain inhibition system, therefore helping the activation of the trigeminal system. It could mediate by acting directly over the cranial vessels, or in central pain control pathways, or by cortical projections of brainstem serotonergic nuclei. [37][38]

Calcitonin gene-related peptide is abundant in trigeminal ganglion neurons. It is released from the peripheral nerve and central nerve terminals as well as secreted within the trigeminal ganglion. When released from the peripheral terminals, it initiates an increased synthesis of nitric oxide and latter sensitization of trigeminal nerves.[39][40] It is a

strong vasodilator of cerebral and dura mater vessels, therefore a component of neurogenic inflammation, and it also mediates trigeminal pain transmission from vessels to the central nervous system.

### 1.1.4 Classification of Migraine

Migraine can be classified into subtypes, according to the headache classification committee of the International Headache Society: [43]

- **Migraine without aura** is a recurrent headache attack of 4 to 72 hours; typically unilateral in location, pulsating in quality, moderate to severe in intensity, aggravated by physical activity, and associated with nausea and light and sound sensitivity (photophobia and phonophobia).
- **Migraine with aura** has recurrent fully reversible attacks, lasting minutes, typically one or more of these unilateral symptoms: visual, sensory, speech and language, motor, brainstem, and retinal, usually followed by headache and migraine symptoms.
- **Chronic migraine** is a headache that occurs on 15 or more days in a month for more than three months and has migraine features on at least eight or more days in a month.

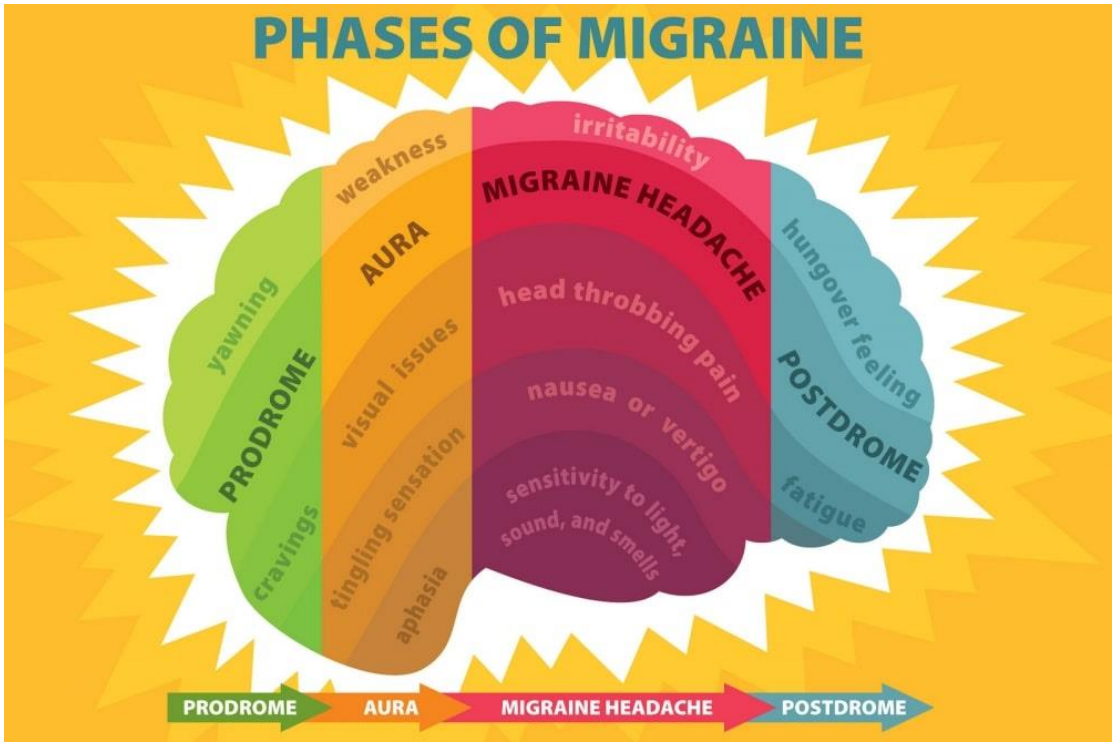


**Figure 1.2** Phases of migraine [44]

**1.1.5 Migraine attacks** occur through four phases:[45]

Prodrome: premonitory symptoms associated with hypothalamus activation (dopamine) [46,47]

- Around 77% of patients suffer prodromic symptoms up to 24 to 48 hours before headache onset. It is more common in females than males (81 to 64%).
- Frequent symptoms are yawning (34%), mood change, lethargy, neck symptoms, light sensitivity, restlessness, difficulties in focusing vision, feeling cold, craving, sound sensitivity, sweating, excess energy, thirst, edema.

- Aura: changes in cortical function, blood circulation, and neurovascular integration. It occurs in about 25% of the cases.[45,48]
  - It can precede the headache, or it can present simultaneously.

- They are typically gradual, with less than 60 minutes of duration, more often visual, and have positive and negative symptoms.
    - Positive symptoms are caused by active release from central nervous system neurons (bright lines or shapes, tinnitus, noises, paresthesias, allodynia, or rhythmic movements).
    - Negative symptoms point out a lack or loss of function (reduction or loss of vision, hearing, sensation, or motion).
- They have to be fully reversible.
- Visual auras are the most frequent ones.
    - The most common positive visual symptom is the scintillating scotoma (an area of absent vision with a shimmering or glittering zigzag border).
    - The most common negative visual symptom is the visual field defects.
- Sensory auras are also common. They can follow visual symptoms or occur without them.
    - It usually consists of tingling sensations on one side of the face or a limb. They are considered paresthesias.
- Language auras are not frequent. They consist of transient dysphasia.
- Motor auras are rare. They consist of complete or partial hemiplegia that can involve limbs and the face.

- Headache: additional changes in blood circulation and function of the brainstem, thalamus, hypothalamus, and cortex.
    - Often unilateral, generally with a pulsatile or throbbing feature and increasing intensity within the first hours.
    - The intensity can correlate to nausea, vomiting, photophobia, phonophobia, rhinorrhea, lachrymation, allodynia, and osmophobia.
    - It can take place over hours to days.
    - Patients may have to seek relief in dark places, as the pain usually resolves in sleep.
- Postdrome: persistent blood changes with symptoms after headache termination.
    - This phase consists of a movement-vulnerable pain in the same location as the previous headache.
    - Common symptoms can be exhaustion, dizziness, difficulty concentrating, and euphoria.

### 1.1.6 Diagnosis

The diagnosis of migraine is based on patient history, physical examination, and fulfillment of the diagnostic criteria. The necessary information that has to be gathered consists of these simple questions: [43]

- Demographic features of the patient: age, gender, race, profession
- When did the headache start?
- Where does it hurt? Location, irradiation.
- What is the intensity of the pain?

- How is the pain? Which are the qualitative characteristics of the pain?
- How long does the pain last?
- In which moment of the day does the pain appear?
- How has it evolved since it started?
- What is the frequency of appearance?
- What are the triggering situations?
- Simultaneous symptoms?
- Is it related to sleep?
- How does it get better or worse?
- Which medications do you take to make it better? What is the frequency of this medication?

The International Classification of Headache Disorders (ICHD-3) describes these diagnostic criteria.[43]

B1. Migraine without aura:

B1a. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)

B1b. Headache has at least two of the following characteristics:

- Unilateral location
- Pulsating quality
- Moderate or severe pain intensity
- Aggravation by or causing avoidance of routine physical activity (walking or climbing stairs)

B1c. During headache, at least one of the following:

- Nausea and vomiting

- Photophobia and phonophobia

B2. Migraine with aura:

B2a. One or more of the following fully reversible aura symptoms:

- Visual
- Sensory
- Speech and language
- Motor
- Brainstem
- Retinal

B2b. At least two of the following characteristics:

- At least one aura symptom spreads gradually over 5 or more minutes
- Two or more aura symptoms occur in succession
- Each aura symptom lasts 5 to 60 minutes
- At least one aura symptom is unilateral
- At least one aura symptom is positive
- The aura is accompanied, or followed within 60 minutes, by the headache.

C. On eight days or more per month for more than three months, fulfilling any of the following:

- Criteria B1b and B1c for migraine without aura
- Criteria B2a and B2b for migraine with aura

- It is believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

D. Not better accounted for by another ICHD-3 diagnosis

**The ICHD-3 criteria for migraine without aura are:**

1. At least five attacks fulfilling criteria B to D (see below)
2. Headache attacks that last 4 to 72 hours, untreated or unsuccessfully treated
3. Headache that has at least two of the following criteria:
    - Unilateral location
    - Pulsating quality
    - Moderate to severe pain intensity.
    - Aggravation by or causing avoidance of routine physical activity (as walking or climbing stairs)
4. During headache, at least one of the following:
    - Nausea, vomiting, or both
    - Photophobia and phonophobia
5. Not better accounted for by another ICHD-3 diagnosis

**The ICHD-3 criteria for migraine with aura are:**

1. At least two attacks fulfilling criteria B to D
2. One or more of the following fully reversible aura symptoms:
    - Visual
    - Sensory

- Speech and language
- Motor
- Brainstem
- Retinal

3. At least three of the following six characters:
    - At least one aura symptom spreads gradually over ≥5 minutes
    - Two or more symptoms occur in succession
    - Each aura symptom lasts 5 to 60 minutes
    - At least one aura symptom is unilateral
    - At least one aura symptom is positive
    - The aura is accompanied, or followed within 60 minutes, by the headache
4. It is not better accounted for by another ICHD-3 diagnosis
5. Hemiplegic migraine is diagnosed when the aura consists of motor weakness.
6. Migraine with brainstem aura (previously known as basilar artery migraine or basilar migraine) is diagnosed if the aura symptoms emerge from the brainstem (bilateral hemianopic visual disturbance, diplopia, vertigo, ataxia, dysarthria, tinnitus, hyperacusis, bilateral paresthesia, or numbness)
7. Retinal migraine is diagnosed when the aura involves a monocular visual field defect.

**The ICHD-3 criteria for chronic migraine are:**

1. Headache (tension-type-like or migraine-like) on 15 or more days per month for more than three months and fulfilling criteria B and C
2. It is occurring in a patient who has had at least five attacks fulfilling the following criteria for migraine without aura (B1) or migraine with aura (B2)

Neuroimaging (computed tomographic scan, magnetic resonance imaging, magnetic resonance angiography, or magnetic resonance venography) is indicated in the following cases: [49,50]

- Acute severe headache, especially if it is the first or worst episode (discard subarachnoid hemorrhage).
- Abnormal neurologic examination, especially if there are unexplained symptoms or signs (confusion, stiff neck, papilledema, epilepsy).
- Non-typical characteristics.
- Changes in the patient's typical features or patterns
- Resistance to treatment.
- New episodes in older (>50 years of age) or immunosuppressed patients.
- Systemic or meningeal signs or symptoms (fever, weight loss, fatigue)

The commonly used acronym "SNOOP" can be used to aid in the determination of neuroimaging indications:

- "S" for systemic signs or symptoms and secondary risk factors
- "N" for neurologic signs or symptoms

- “O” for onset
- “O” for older
- “P” for position-dependent intensity changes, prior pattern changes, papilledema, and precipitated by Valsalva maneuvers.

Cerebrospinal fluid analysis and electroencephalogram are not typically performed unless seizure activity of infectious etiology has to be excluded.

### 1.1.7 CLINICAL MANIFESTATIONS

Migraine is characterized by episodes of head pain that is often throbbing and frequently unilateral and may be severe. In migraine without aura (previously known as common migraine), attacks are usually associated with nausea, vomiting, or sensitivity to light, sound, or movement.[51] When untreated, these attacks typically last 4 to 72 hours.[52] A combination of features is required for the diagnosis, but not all features are present in every attack or in every patient. These symptoms distinguish migraine from tension-type headache, the most common form of primary headache, which is characterized by the lack of associated features.

Any severe and recurrent headache is most likely to be a form of migraine and to be responsive to antimigraine therapy.[53] In 15 percent of patients, migraine attacks are usually preceded or accompanied by transient focal neurologic symptoms, which are usually visual; such patients have migraine with aura (previously known as classic migraine). [54] In a recent large, population-based study, 64 percent of patients with migraine had only migraine without aura, 18 percent had only migraine with aura, and 13 percent had both types of migraine (the remaining 5 percent had

aura without headache) . Thus, up to 31 percent of patients with migraine have aura on some occasions, [55] but clinicians who rely on the presence of aura for the diagnosis of migraine will miss many cases. We find it useful to assess the severity and effects of migraine by asking about time lost because of migraine at work or school, in performing household work or chores, or in family, social, and leisure activities. One can ask patients directly about temporary disability, have them keep a diary, or get a quick but accurate estimate with the use of the Migraine Disability Assessment Scale (MIDAS), a well validated five-item questionnaire that is easy to use in practice.[56]

A recent survey by the World Health Organization (WHO) rates severe migraine, along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disorders. [57] This ranking suggests that in the judgment of the WHO, a day with severe migraine is as disabling as a day with quadriplegia.

### 1.1.8 Triggers

Withdrawn or exposed to several factors contribute to the development of migraine headaches.[58] A retrospective study found that 76% of the patients reported triggers.[59] Some of them are probable factors that contribute, while others are only possible or unproven factors.Stress (probable factor)

Hormonal changes during menstruation, ovulation, and pregnancy (probable factor)

Skipped meals (probable factor)

Weather changes in (probable factor)

Excessive or insufficient sleep (possible factor)

Odors (perfumes, colognes, petroleum distillates)

Neck pain in

Exposure to lights in (probable factor)

Alcohol ingestion (wine as a probable factor)

Smoking (unproven factor)

Late sleeping in

Heat ,Exercise

Food in (aspartame as a possible factor, and tyramine and chocolate as unproven factors)

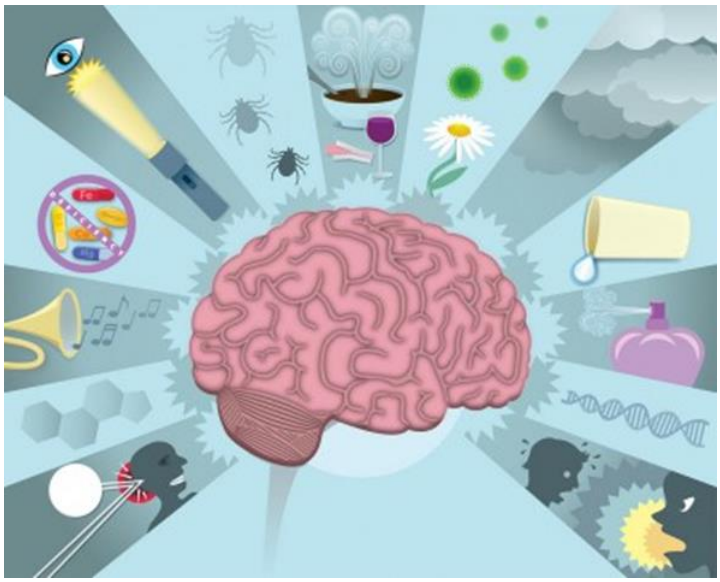

**Figure 1.3 Migraine triggers [32]**

### 1.1.9 Treatment

Treatment options are based on the onset scenarios: acute or chronic.

**Acute or Abortive treatment**

- Acute treatment aims to stop the progression of a headache. It has to be treated quickly, and with a large single dose. Oral agents can be ineffective in patients with migraine-induced gastric stasis. For that reason, parenteral medication could be the rule for some patients, especially the ones with nausea or vomiting. Therapy consists of stratified options:[60,61,62]
    - NSAIDs (nonsteroidal anti-inflammatory drugs): ibuprofen, naproxen, diclofenac, aspirin, or acetaminophen. Usually in mild to moderate attacks without nausea or vomiting.
    - Triptans (the first-line in patients with allodynia): sumatriptan, eletriptan, rizatriptan, almotriptan. With or without naproxen for moderate to severe attacks.
        - Triptans should be limited to less than ten days of use within a month to avoid medication overuse.
        - Because of the activation of the 5-HT(1B) and 5-HT(1D) receptors on coronary arteries and cerebral vessels, there are recommendations against its use in patients with ischemic stroke, ischemic heart disease, poor-controlled hypertension, angina, pregnancy, hemiplegic or basilar migraine. In these patients, with cardiovascular risks, the best-suited medication is a selective serotonin 1F receptor agonist that does not produce vasoconstriction; lasmiditan.
        - It is recommended to monitor therapy if the patient takes selective serotonin reuptake inhibitors or selective serotonin-noradrenaline reuptake inhibitors because of the risk of serotonin syndrome.

- Antiemetics: metoclopramide, chlorpromazine, prochlorperazine. They are generally used as adjunctive therapy with NSAIDs or triptans to decrease nausea and vomiting, especially in the emergency department. Diphenhydramine can also be added to prevent dystonic reactions (mostly with metoclopramide).
- Calcitonin-gene-related peptide antagonists: rimegepant, ubrogepant. It could be considered in patients that don't respond to conventional treatment or in those with coronary artery disease.[63]
- Ergots: ergotamine and dihydroergotamine, being this last one the only one recommended for acute attacks as a parenteral administration, and effective as bridge therapy for medication overuse headache and status migrainosus. Ergotamine has not demonstrated particular effectiveness yet, and it can present significant side effects.
- Dexamethasone can reduce the recurrence of early headaches, but does not provide immediate relief of headaches.[64,65]
- Transcutaneous supraorbital nerve stimulation can reduce intensity.[66]
- Transcranial magnetic stimulation is proved effective as a second-line treatment, with no serious side effects. It can also be offered as an option to treat chronic migraines. It is contraindicated in patients with epilepsy. [67,68,69]
- Nonpainful remote electric neurostimulation could be considered as a first-line treatment in some patients.[70,71]

- Peripheral nerve blocking (occipital plexus and sphenopalatine ganglion).[72,73]
- Botulinum toxin Since botulinum toxin might have a therapeutic effect on pain, many studies investigating the efficiency of botulinum toxin in headache treatment have been done. The most satisfying results were achieved by botulinum toxin type A (BoNT/A) in the treatment of chronic migraine. In this paper, we reviewed the clinical effectiveness of BoNT/A in migraine and included in clinical experience. In ongoing pilot study, where we have repeated BoNT/A injections every 12 weeks.[74]

  People with chronic (persisting) migraine treated with botulinum toxin injections had two fewer migraine days per month than people treated with placebo (fake treatment). It is unclear if this improvement was large enough to make a meaningful difference to their lives. More work is needed to show whether botulinum toxin is better than oral treatments (treatments that are swallowed), that prevent migraine. The evidence for botulinum toxin for people with episodic (occasional) migraine was uncertain. Treatment with botulinum toxin did not cause many side effects.[75]

- **1.1.10 Prophylactic or Preventive Treatment**

Preventive treatment aims to reduce attack frequency and to improve responsiveness to acute attacks' severity and duration, and reduce disability.[76,77] Migraine triggers have to be documented by each individual to reduce them in the future.

When migraines become so frequent or severe that they interfere with work or usual activities, it is time to consider using preventive strategies. If acute medications are being used more than 2 days per week, this alone can lead to more headaches, sometimes called rebound or medication overuse headaches, and the only way out of .this quagmire is to start a preventive strategy

Prevention is not a cure. It is highly likely that migraines will continue to occur, and in fact a preventive may be considered successful if the frequency, severity, and/or intensity of the headaches are cut in half. There is no preventive strategy known that does not have the potential for side effects, but this must be balanced against the possible gain from feeling better, and being able to work, play, and generally function more normally without relying too much on ongoing acute medications.

- Indications for preventive treatment are:
  - Frequent or long-lasting headaches
  - Attacks that cause significant disability and reduced quality of life
  - Contraindication or failure to acute therapies
  - Significant adverse effects of abortive therapies
  - Risk of medication overuse headache
  - Menstrual migraine (along with short-term premenstrual prophylaxis)
  - Hemiplegic migraine
  - Brainstem aura migraine
  - Persistent aura without infarction

        - Migrainous infarction
    - Preventive treatment agents are the following:
        - Beta-blockers: metoprolol and propranolol. Especially in hypertensive and non-smoker patients.
        - Antidepressants: amitriptyline and venlafaxine. Especially in patients with depression or anxiety disorders, and insomnia.
        - Anticonvulsants: valproate acid and topiramate. Especially in epileptic patients.
        - Calcium channel blockers: verapamil and flunarizine. Especially in women of childbearing age or patients with Raynaud's phenomenon.
        - Calcitonin gene-related peptide antagonists: erenumab, fremanezumab, and galcanezumab.

### 1.1.11 Prognosis

A migraine is a chronic condition that can revert to episodic migraine in 26 to 70% of patients. Prolonged remissions are common; however, some patients have a pattern of leaving and returning to chronic states. The severity and frequency of attacks can diminish with age.[78] Episodes increase during puberty but continue to climb until 35 to 39 years of age, decreasing later in life, especially after menopause.[79]

### 1.1.12 Complications

These complications can be serious enough to send patients to the hospital or leave them simply uncomfortable or queasy: **[**80**]**

**Status Migrainosus**

It's Latin for a migraine that just won't go away. Most migraines usually linger between 4 and 72 hours. Status migrainosus, on the other hand, is a relentless attack that lasts for more than 3 days. It can leave feeling drained or even disabled. You may need care at the hospital. This type of migraine often comes on after you take too much headache medication.

**Migrainous Infarction**

Also called a migrainous stroke, this is a rare complication that happens mostly in younger women. Blood vessels to the brain can get narrowed and cut off the oxygen supply. A migrainous stroke can hit suddenly and is an emergency. It always happens with an aura, a set of unusual sensations like flashes of light, blind spots, and tingling hands or face.

**Persistent Aura Without Infarction**

One in four people with migraines can have aura. But sometimes it lingers for more than a week after an attack. Rarely, you can have aura and symptoms like trouble breathing and numbness for months or even years.

The signs can seem close to those of a stroke, or bleeding in the brain, but without any actual bleeding. Infarction is another word for stroke.

**Migraine-Triggered Seizure**

This rare case can look like an epileptic seizure. It happens during or soon after a migraine with aura. Epilepsy and migraine sometimes go together. But researchers don't fully understand why.

**Depression and anxiety**. People who have migraines are much more likely to also have these two conditions than others. That may happen

because of the headaches, or because depression or anxiety leads to migraines.

**Vertigo**. It makes you feel dizzy, or like you're spinning and your balance is off. Vertigo happens more often during migraines in people who are prone to motion sickness.

**Sleeplessness**. The pain and discomfort of migraines can keep you from falling or staying asleep. You also may wake up too early or don't feel refreshed. Insomnia is worse in people who get severe migraines and more often.

**Nausea and vomiting**. These are common migraine symptoms. Reasons may have to do with the brain chemical serotonin, aka the "feel-good" hormone. People who get migraines may have low serotonin levels, which researchers suspect is linked to motion sickness and symptoms like nausea.

**Serotonin syndrome**. Drugs called triptans can treat migraine attacks, but you shouldn't take them every day. They can interact with other medications, like common antidepressants, that raise your serotonin levels. That can cause serious complications like agitation, confusion, diarrhea, twitchy muscles, and a racing heart.

**Stomach problems**. You can take over-the-counter pain relievers like aspirin or ibuprofen for migraines. But they and other non-steroidal anti-inflammatory drugs (NSAIDs) can cause ulcers, stomach pain, or bleeding if you take too much or for too long.

**Rebound headaches**. This is another medication-related complication. Some migraine meds -- particularly ones that have caffeine (ergot) -- can worsen your headache. So can acetaminophen, combination pain relievers such as Excedrin, and sleeping pills when taken too often.

## 1.2 Botulinum Toxin

### 1.2.1 Definition

Botulinum toxins A and B, which are produced by the bacterium Clostridium botulinum, are used for the treatment of facial rhytides (for example, lateral orbital wrinkles, lower eyelid wrinkles, and labial lines), by producing weakness or paralysis of the associated muscles, and in the treatment of hyperhidrosis. The toxin binds with high affinity to peripheral cholinergic nerve endings, such as those at the neuromuscular junction and in the autonomic nervous system, preventing the release of the neurotransmitter acetylcholine. This action at the neuromuscular junction can cause weakness and even paralysis of the muscles supplied by the affected nerves. Sprouting of the terminal nerves eventually results in re-innervation of the muscles and return of function. Doses are measured in mouse units (MU), 1 MU being the LD50 in Swiss–Webster mice.

Botulinum toxin is used in the treatment of excessive muscle contraction disorders (dystonias), such as strabismus, blepharospasm, focal dystonias, and spasticity. One of its uses is in the removal of facial wrinkles by paralysing mimic muscles. It can reduce sweat production by blocking cholinergic innervation of eccrine sweat glands, Botulinum toxin type A is established as useful in headache prophylaxis and several other neurological conditions.[81]

### 1.2.2 Nomenclature

Although botulinum toxin is commonly known as “Botox”, that name is in fact only one of the brand names of formulations in which botulinum toxins are available. For example, in the UK, the following branded formulations are available:

- botulinum toxin type A: Bocouture (50-unit vials), Vistabel (50-unit vials), Xeomin (100-unit vials)
- botulinum toxin type A-hemagglutinin complex: Azzalure (125-unit vials), Botox (50-unit vials), Dysport (500-unit vials)
- botulinum toxin type B: Neurobloc (5000 units/ml in vials containing 0.5, 1, or 2 ml).

The established drug names have also been changed, in order to reinforce individual potencies and prevent medication errors. The new name to replace “botulinum toxin type A” is OnabotulinumtoxinA (marketed as Botox and Botox Cosmetic). The name that replaces to “botulinum toxin type B” is RimabotulinumtoxinB (marketed as Myobloc).[81]

### 1.2.3 History

The history of botulinum toxin (BoNT) dates to 1817, when Christian Andreas Justinus Kerner first recognized that food-borne botulism was due to a toxin that paralyzed skeletal muscles and parasympathetic function. He proposed the term botulinum toxin and suggested that it could be used to treat involuntary spasms and movements. In 1895, Emile Van Ermengem first isolated the bacterium clostridium botulinum after an outbreak following a funeral ceremony in the Belgian village Ellezelles. Edward Schantz first cultured Clostridium botulinum and isolated the toxin in 1944, and in 1949, Burgen and his colleagues found that BoNT blocked neuromuscular transmission by blocking the release of acetylcholine.[82]

The first report of clinical application of BoNT was published in 1984, when it was demonstrated to be safe and effective in the treatment of blepharospasm. Subsequent double-blind, placebo-controlled, and open-label studies provided evidence that BoNT was a powerful therapeutic tool in a variety of neurologic and other disorders. Although its widest application is still in the treatment of disorders manifested by abnormal, excessive, or inappropriate muscle contractions, its use is rapidly expanding to include the treatment of a variety of ophthalmologic, gastrointestinal, urologic, orthopedic, dermatologic, secretory, painful, and cosmetic disorders. [83]

### 1.2.4 Mechanism of Action

The peripheral nervous system, composed of an extraordinary number of nerves, networks, and synaptic connections, is extremely complex. However, botulinum toxin exerts its effects by acting at only one type of site in this complex system. The toxin acts only on those nerve endings that store and release the transmitter substance acetylcholine. Nerve endings that use acetylcholine as a transmitter are called cholinergic. Botulinum neurotoxin acts on all cholinergic cells to block the release of acetylcholine. Blockade of transmission between motor nerves and voluntary muscles causes paralysis.[84]

With time, nerve sprouting occurs and new neuromuscular junctions are formed. Also, the intoxicated neuron gets reactivated after a period of time specific to each serotype. As a result, the neuron returns to the previous clinical state. Hence the effects of botulinum toxin are fully reversible.[83] When injected, the various preparations of BoNT produce local, temporary and reversible cholinergic chemodenervation of muscles and glands.[85] Botulinum toxin A is preferred because of its long duration of action and ease of production. [83] In addition to

chemodenervation, BoNT/A has also been shown to modify the sensory feedback loop to the central nervous system through effects on the muscle spindle and has anti-nociceptive effects in experimental models. [85] Immune responses to BoNT/A and presumably other BoNT preparations can be minimized by using the least required dose and avoiding frequent repeat injections.[83] Current labeling in most countries suggest 12-week separation between doses of BoNT.

Clinical effect of the serotype A and B toxins begins within 24-48 hours, peaks at 2-3 weeks and lasts for 3-4 months.[83],[85] Therapeutic window of a muscle refers to the suitability of a target muscle for BoNT therapy. Botulinum toxin reduces both voluntary and dystonic strength of a muscle. Functional impairment can be avoided by reducing the voluntary strength within the range of its reserve strength. Thus reserve strength of the muscle determines therapeutic window. Finger flexors and extensors and muscles of the lower half of the face have a narrow therapeutic window and hence have higher chances of functional impairment when injected. Orbicularis oculi muscle has wider therapeutic window. [83]

### 1.2.5 Side effects

Reduction of physiological strength is an obligatory side effect, yet, is uncommon due to a wide therapeutic window and presence of agonist muscles.[83] Side effects can either be local transient weakness due to spread to adjacent muscles or systemic spread of unbound BoNT. Systemic spread of botulinum toxins is not expected to result in clinical effects and for type A toxin, is often seen at the level of single fiber EMG studies as jitter in distant muscles. BoNT/B does however produce dry mouth from distal injections and may be due to either more easy systemic absorption or higher affinity for autonomic nerve endings. Usually less

than 5% is absorbed and, when BoNT is used in therapeutic doses, manifestations of systemic spread are rare.[83] The non-toxin proteins in the injections can occasionally cause flu-like symptoms. [83] Action of all BoNTs are believed to be enhanced by aminoglycoside antibiotics.[83] Calcium antagonists may inactivate BoNT. Botulinum toxin should be avoided in pregnancy, in patients with neuromuscular transmission disorders and in impaired hemostasis.[83]

### 1.2.6 Potential Risks

Botulinum toxin is generally considered to have a wide safety margin. [86] however, there are inherent risks. The risks fall into three categories :that include

1.Reactions to the medication

2.Overdosing

3.Poor injection technique

Reactions to the Medication

Allergic reactions to botulinum toxin are very rare. Botox hypersensitivity reactions have been reported to include anaphylaxis, urticaria, soft tissue edema, and dyspnea. One fatal case of Botox and lidocaine together was reported, although it is not certain which drug caused the reaction.[87] In individuals with preexisting neuromuscular disorders (e.g., amyotrophic lateral sclerosis, myasthenia gravis, and Eaton–Lambert syndrome), it is recommended that botulinum toxin be used with caution because there have been cases of systemic sensitivity with resultant dysphagia and respiratory compromise.[87] Dysphagia may also occur more locally when botulinum toxin is used in the paracervical region. In people who are taking aminoglycosides or other drugs that

interfere with neuromuscular transmission (e.g., curare-like compounds), botulinum toxin should be used with caution because it may potentiate the effects of these drugs. Localized reactions may occur in the first 2 weeks and are similar to those of other injections, including pain, swelling, tenderness, and bruising at the injection site. These are usually transient and do not require medical intervention.

Overdosing

Because botulinum toxin causes functional weakness (you can think of this as a localized paralysis or partial paralysis of the injected muscle), it makes sense that injecting too much can “overparalyze” a region and lead to significant problems. Examples include the unintended paralysis of facial muscles, problems with dysphagia, and excessive limb weakness. Because the effects do wear off, this is not a permanent problem, but it can be quite debilitating during the time that the drug is in effect. A longer discussion with dosing recommendations can be found in Chapter

Poor Injection Technique

Botulinum toxin should be delivered only to muscles; therefore, it is important to aspirate and be sure that you are not injecting into a blood vessel. Poor injection technique may lead to injury to an organ or nerve. Another technique problem occurs if the wrong muscle is injected and you do not get the desired effect. In addition, you may induce weakness in a muscle that you did not intend.

In general, botulinum toxin is a relatively safe and easy medication to inject. It can provide significant pain relief for many weeks to patients who are suffering. However, it should be considered only after conventional pain treatments have been tried and failed. Moreover, it is

important to pay particular attention to dosing and ensure that you are injecting into the appropriate muscle.

### 1.3.1 Botulinum Toxin in the Treatment of migraine

Nowadays, a variety of clinical medications, including β-blockers, antiepileptic drugs, calcium antagonists, antidepressants, calcitonin gene-related peptide (CGRP), and onabotulinumtoxinA (BoNT-A), are utilized to prevent migraine [88,98].

Initially, it was hypothesized that the mechanism of pain relief by this toxin is due to muscle relaxation and subsequent hypotension [90]. Several mechanisms have been proposed regarding the function of BoNT-A, including inhibiting the exocytosis of neurochemicals and proteins of the motor and sensory systems, reducing exocytosis of proinflammatory cells, neurotransmitters, and excitatory neuropeptides of the nervous system such as substance P, CGRP, glutamate, and inhibiting soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) [91]. Recent experimental studies have shown that BoNT-A may influence the central nervous system (CNS). The toxin was initially used to treat dystonia and blepharospasm, but following two controlled clinical trials, it was later approved that BoNT-A can also prevent migraine [92]. In these studies, known as the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT), it was found that BoNT-A injection, compared with placebo, affected the frequency and severity of chronic migraine (CM) and alleviated symptoms. The most common side effects observed after the injection included neck pain,

muscle weakness, and pain in the injection site. Repeating this treatment showed that the use of BoNT-A was safe and well tolerated [93].

The practical guidelines for the use of BoNT-A in the treatment of CM, presented by the European Headache Federation (EHF), recommended that 155–195 units should be repeated in the form of intramuscular injection in 31–39 areas around the head and neck at 12-week intervals. Patients should preferably try some other strategies for preventing migraine before starting treatment with BoNT-A [94]. On the other hand, the cost-effectiveness of BoNT-A treatment is an important factor for both the individual and the community. According to the calculations of the National Institute for Health and Care Excellence (NICE), using this method is cost-effective [95].

Why Do We Need Another Drug For Treatment Or Prophylaxis In Primary Headache Disorders? Headache can be debilitating, causing lost productivity at work or school, impaired quality of life, and disruptions in family and social life. Moderate-to-severe adverse events are common with the available preventive medications. Tricyclic antidepressant use is associated with sedation, weight gain, dry mouth, nausea, constipation, dizziness, mental confusion, palpitations, blurred vision and urinary retention (96,97). b-blockers are associated with drowsiness, fatigue, lethargy, sleep disorders and depression whereas calcium channel blockers can cause constipation, peripheral edema and weight gain (96,97). Therefore any preventive measure that is more effective and associated with fewer side effects is apparently needed in primary headache disorders.

### 1.3.2 Botulinum Toxin And Its Actual Mechanism Of Effect

Botulinum toxin type A and type B have been used for research purposes clinically for headaches. Botulinum toxin type A (BotoxR) [98] or botulinum toxin type B (MyoblocR) [99]. These two products have different dosing, safety and efficacy characteristics. There is no established methodology to calculate equivalent doses. [100]

Number of studies using botulinum toxin B for the prophylaxis and treatment of headaches is rare compared to botulinum toxin A[101,102]

The most commonly used formulation of Botulinum neurotoxin type A is BotoxR and as a drug it is a purified neurotoxin complex, in a sterile, vacuum-dried and purified form, produced from fermentation of Hall strain Clostridium botulinum type A grown in a medium containing casein hydrolisate, glucose and yeast extract. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin and several accessory proteins. Each vial of BotoxR contains 100 Units (U) of Clostridium botulinum type A neurotoxin complex, 0.5 milligrams of Albumin (Human) and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative. [103]

In migraine type of headache it has been proposed that factors other than a decreased pericranial muscle tension play an important role in the mechanism of the effect of BotNT-A, since the pain relief following BotNT-A injections in migraine headache may well outlast the duration of effect of the drug itself. [100,104] Current pathophysiological models of migraine focus on the trigeminovascular system as an important generator of the sensory input leading to migraine. According to this model, trigeminal afferents innervating meningeal vessels are activated during migraine possibly by a wave of neuronal depression that spreads across the cerebral cortex . [105] Consequently afferents in ophthalmic

branch (V1) of the trigeminal nerve are stimulated to release various neuropeptides, including calcitonin gene-related peptide (CGRP). BotNT-A has been shown to directly inhibit the CGRP secretion from stimulated trigeminal neurons in an experimental model. [106] Previous studies have shown that BotNT-A inhibits the release of substance P (mediated by cleavage of the intracellular effector SNAP-25) and glutamate, another neurotransmitter involved in nociceptive processing.[96,107] As a result beyond chemodenervation of skeletal muscle BotNT-A inhibits neurotransmission of pain signals from periphery to cortex.

### 1.3.3 Choosing The Appropriate Candidate For BotNT-A Injection

Although there is no consensus on the standards for application of BotNT-A in preventing certain types of primary headaches (most commonly migraine and tension-type headache), results from clinical studies have revealed a patient population which may be more appropriate for BotNTA application.

Candidates for Botulinum Toxin Type A Therapy for Headache [100]

• Patients with disabling primary headaches

• Patients who have failed to respond adequately to conventional treatments • Patients with unacceptable side effects (from existing treatments)

• Patients in whom standard preventive treatments are contraindicated

• Patients in special populations or situations (the elderly, those at risk of unacceptable side effects from trial drugs or traditional treatments, airplane pilots, students studying and preparing for examinations)

• Patients misusing or abusing or overusing medications

• Patients with coexistent jaw, head or neck muscle spasm

• Patients who prefer this treatment

### 1.3.4 Injection Techniques And Sites For BotNT-A

BotNT-A is used in the range of 50 to 100 units for all types of headache. The technique of delivering small doses at multiple sites reduces the occurrence of side effects and controls head pain efficiently. To achieve this, a dilution of 4 mL of normal saline to 100 units of BotNT-A is used. The dose at each site is 2,5 (0.1 cc) to 10 units (0.4 cc).

Number of injected sites may vary from 10 to 25. [104] The injections are administered intramuscularly to limit discomfort and side effects imported by soft tissue diffusion. Intradermal injections may produce similar clinical improvement but tend to be more uncomfortable. [108] Treatment with a fixed-site approach rather than follow-the-pain approach is recommended for patients with migraine or migrainous headache, because the latter may produce a suboptimal cosmetic outcome and the headaches may shift to the previously unaffected side. [108] The fixed-site approach consists of bilateral injections even if the patient has strictly unilateral headaches. The muscles injected are the procerus, corrugators, frontalis and temporalis.

Follow-the-pain approach is more commonly used in chronic-tension type or chronic daily headache patients. Follow-the-pain injection sites include; the frontalis, temporalis, occipitalis, trapezius, splenius capitis, suboccipital and cervical paraspinal muscles (Figures 1, 2 and 3). Injection sites are identified by history (‘Where does it hurt when you have a headache?’) and (‘Show me with your hands where the pain is’) and by examination of the cervical shoulder girdle and temporomandibular musculature. The doses injected in the cervical

shoulder girdle muscles are kept low, so as to prevent any possible weakness [100,108]

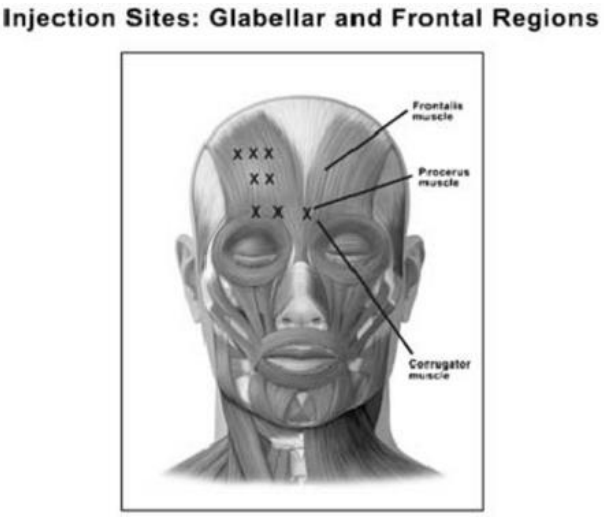


Figure 1.4 BotNT-A injection sites for headache; procerus, corrugator and frontalis muscles.[100]

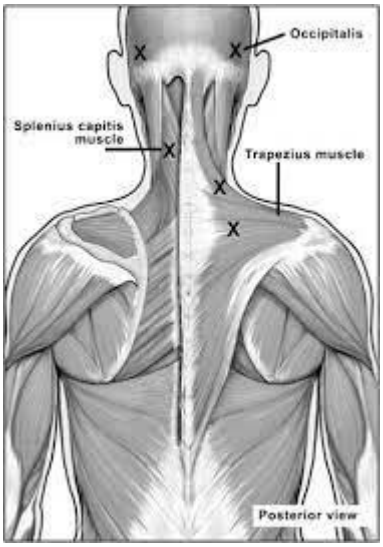


Figure 1.5 BotNT-A injection sites for headache; occipitalis, splenius capitis and trapezius muscles. [100]

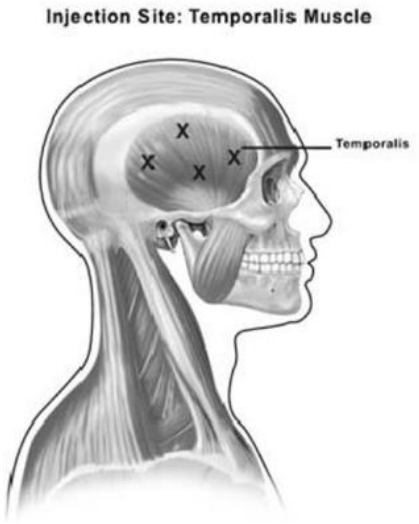


Figure 1.6 BotNT-A injection sites for headache;
temporalis and masseter muscles. [100]

### 1.3.5 Side Effects And Other Important Points For Pre-Warning The Patients And Obtaining An informed Consent

Physicians should review the known side effects of BotNT-A treatment, including possible headache, rash, bruising or eyebrow and eyelid ptosis with the patient and obtain informed consent. Out of 92 patients receiving BotNT-A into the temporalis muscle 26 patients have been reported to develop ‘hourglass deformity’ characterized by bilateral depression of the temporal region ranging from minimal to significant resembling an ‘hourglass’. [109] Patients should also be told that multiple treatment cycles may be needed to achieve an optimal therapeutic effect. [100, 110] However owing to the potential risk of antibody development, BotNT-A treatments should not be repeated more frequently than every 3 months. [111]

### 1.3.6 Botulinum toxin versus placebo

Botulinum toxin may reduce the number of migraine days per month in the chronic migraine population by 3.1 days (95% confidence interval (CI) -4.7 to -1.4, 4 trials, 1497 participants, low-quality evidence). For the population of both chronic and episodic migraine participants a reduction in severity of migraine rated during clinical visits.[112]

### 1.3.7 Botulinum toxin versus other prophylactic agent

Individually trials reported no differences between groups for a variety of efficacy measures in the population of both chronic and episodic migraine participants. The global impression of disease measured using Migraine Disability Assessment (MIDAS) scores were reported from two trials that showed no difference between groups. Compared with oral treatments, botulinum toxin showed no between-group difference in the risk of adverse events.The relative risk reduction (RRR) for withdrawing from botulinum toxin due to adverse events compared with the alternative prophylactic agent was 72% (P = 0.02, 2 trials, N = 119).[112]

### 1.3.8 Prognosis

A double-blind, randomized, 90-day placebo-controlled study that enrolled 30 adult migraineurs. Patients received 50 units botulinum toxin type A (n=15) or placebo (n=15). Outcome measures were monthly frequency and duration of migraine attacks and the number of severe attacks. Botulinum toxin type A produced significantly greater reductions in the frequency of migraine attacks of any severity at Day 90 (-3.14 vs. -0.53; $p<0.05$) and in the frequency of severe migraine attacks at Days 60

(-1.4 vs. -0.54; p<0.05) and 90 (-1.8 vs. -0.20; p<0.02). One patient in the botulinum toxin type A group experienced mild, transient frontalis muscle weakness lasting approximately 30 days. Botulinum toxin type A injections were well tolerated and provided effective migraine prophylaxis in these patients. [113]

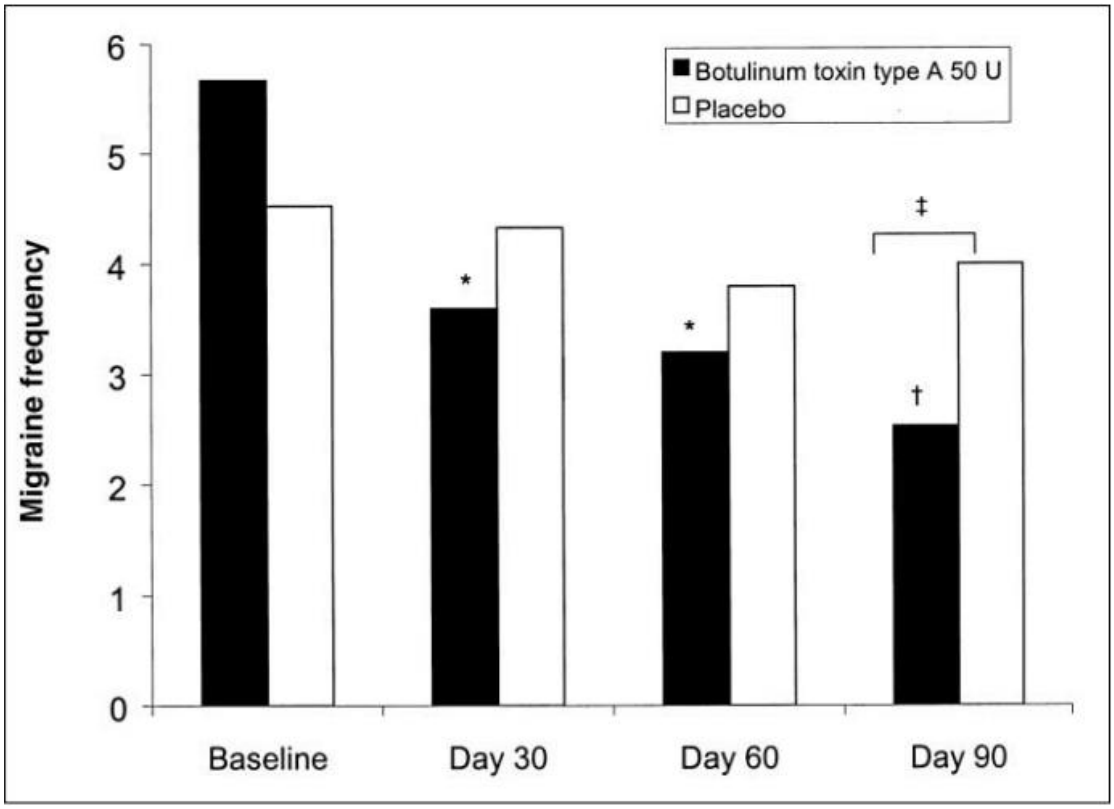


Figure1.7 Frequency of migraine attacks of any severity (mean number per month). botulinum toxin type A vs. placebo. [113]

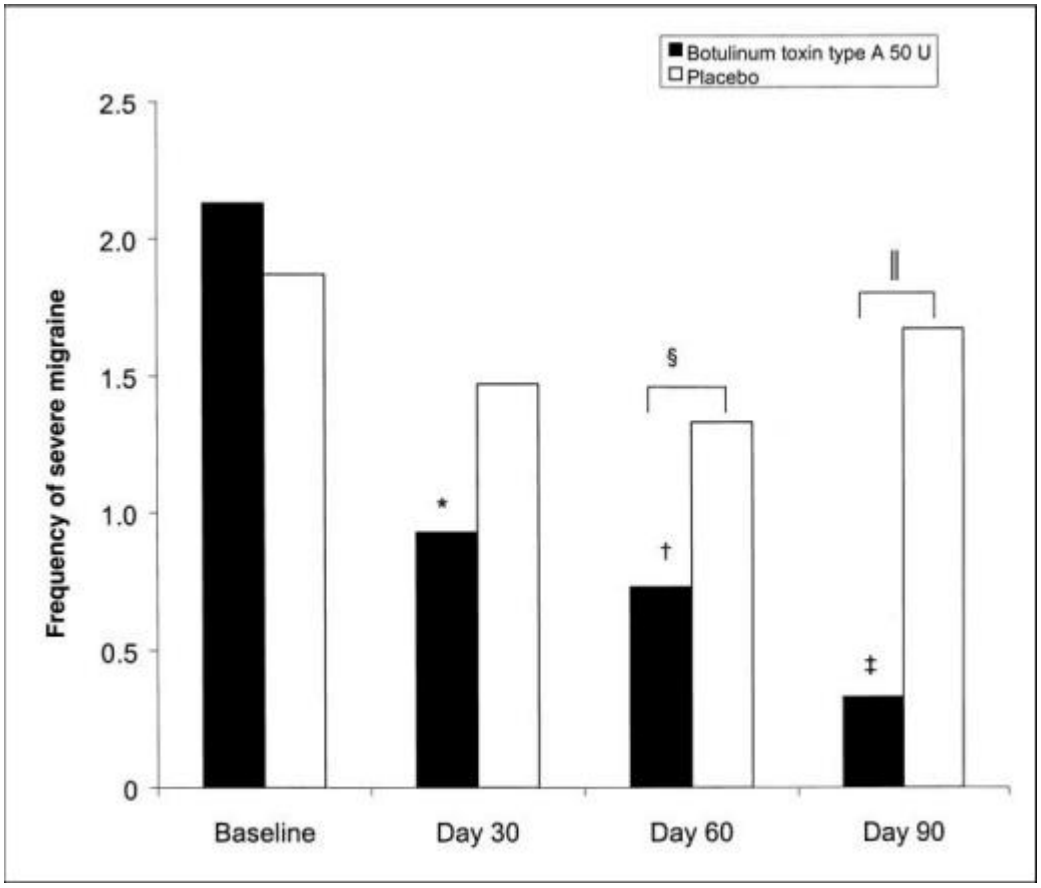


Figure 1.8 Frequency of severe migraine attacks

(mean number per month). botulinum toxin type A vs. placebo. [113]

### 1.3.9 Conclusions

In chronic migraine, botulinum toxin type A may reduce the number of migraine days per month by 2 days compared with placebo treatment. Non-serious adverse events were probably experienced by 60/100 participants in the treated group compared with 47/100 in the placebo group. For people with episodic migraine, we remain uncertain whether or not this treatment is effective because the quality of this limited evidence is very low. Better reporting of outcome measures in published trials would provide a more complete evidence base on which to draw conclusions.[112]

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