Dr Garsing Wong

Sapphire Appearance Medicine Clinic

Auckland

Dr Murray Hing

Flexa Group

Auckland

Chronic Migraine Treatment with Botox and Physio - Concurrent Workshop Repeated

Sunday, 23 June 2013	Start 8:30am	Duration: 55mins	Picasso
	Start 9:35am	Duration: 55mins	Picasso

Chronic Migraine Treatment using Botulinum Toxin Type A

GP CME Workshops 23 June 2013

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Disclosures

- Former Exec Member of the New Zealand College of Appearance Medicine
- Former Chairman of the College of Urgent Care Physicians
- Consultancy with Allergan, Sanofi-Adventis, Valeant, GlaxoSmithKline, Merck Sharpe & Dhome, Palomar Medical Technologies, Bayer, Eli Lilly, Lundbeck, Q-med, Ministry of Social Development
- Research Grants from Glaxo Smith Kline & Bayer

Migraine: more than just a headache

- Occasional headaches are common and are often regarded by most people as part of normal life
- For some, however, headache disorders such as migraine can cause disability and impaired quality of life
- Globally, it is estimated that 46% of the adult population have an active headache disorder[1]

1. Stovner LJ *et al*. *Cephalalgia* 2007;**27**:193−210.

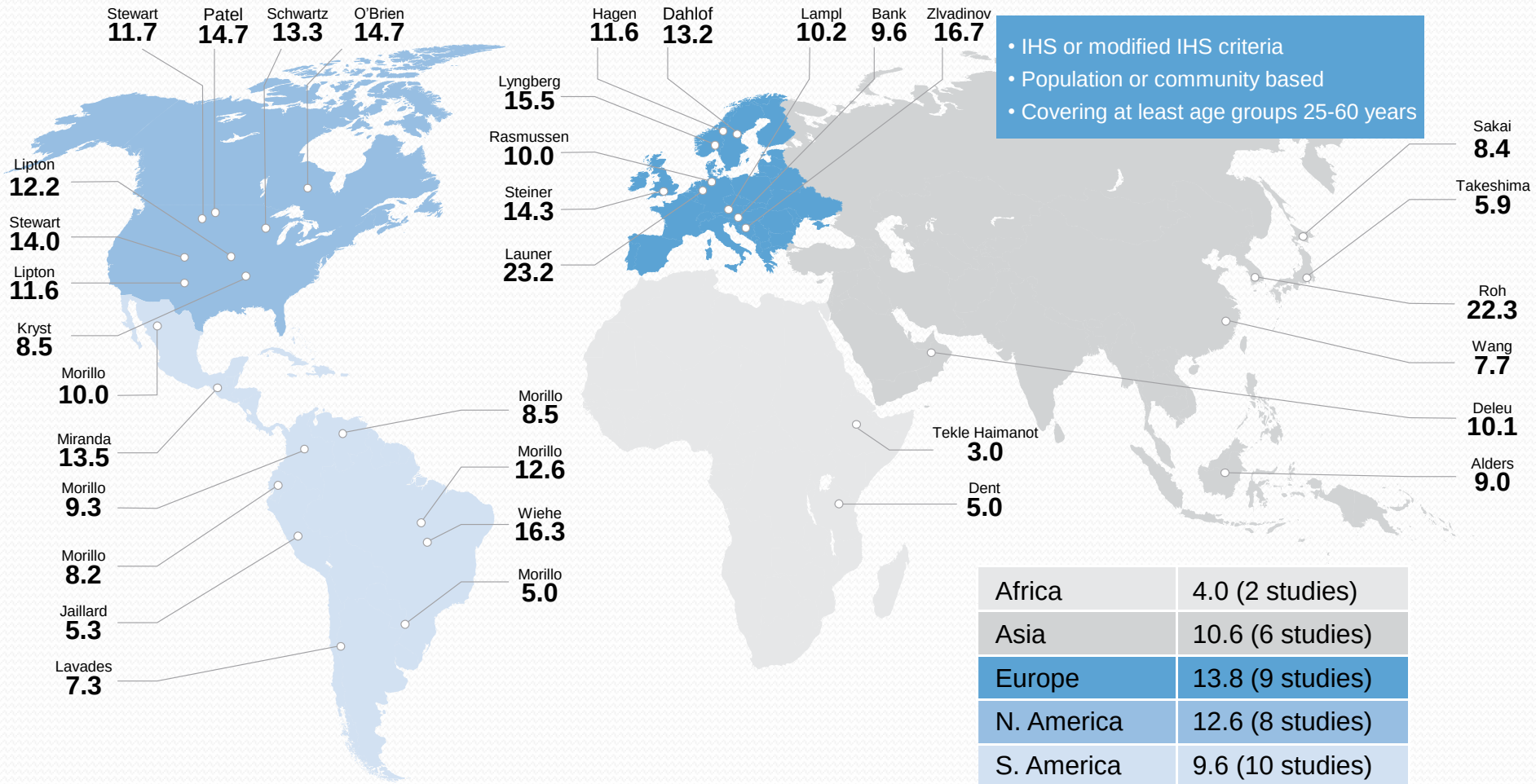
The economic cost of migraine

- Migraine is an important public health problem that is associated with substantial costs[1–3]

Direct costs	Indirect costs
Medication	Absence from work (absenteeism)
Consultation	Reduced productivity at work (presenteeism)
Hospital admission	Lost career opportunities
Diagnostic investigations	Unemployment

1. Steiner TJ *et al*. *Cephalalgia* 2003;**23**:519–527.
2. Hawkins K *et al*. *Headache* 2008;**48**:553−563.
3. Stewart WF *et al*. *JAMA* 2003;**290**:2443−2454.

The global prevalence of migraine is approximately 10%[1]



Africa	4.0 (2 studies)
Asia	10.6 (6 studies)
Europe	13.8 (9 studies)
N. America	12.6 (8 studies)
S. America	9.6 (10 studies)

Mean: 11.2; **Median:** 10.2

1. Stovner LJ *et al. Cephalalgia* 2007;**27**:193–210.

No Prevalence Studies of Chronic Migraine in New Zealand

- Dr Sheena Aurora, Neurologist, Director of the Swedish Headache Centre in Seattle estimates the prevalence in New Zealand to be 1.3%
- 3% episodic migraines->chronic migraine
- Pop 4.4mill -> 80% over age of 15 (Min of Bus Inn)
- estimate 45,814 kiwis suffer from Chronic Migraine!
- Total GP's 3541 (www.healthworkforce.govt)
- 12.9 Chronic Migraine sufferers per GP

Outline

- Prevalence
- How to diagnose Migraine
- Definition of Chronic Migraine
- What do I do for any headache patient SNOOP4
- Botulinum Toxin type A or OnabotulinumtoxinA
- Safety
- What do I do?
- What can you do
- Role of Physiotherapy & Case Presentation – Hand over to Murray Hing

IHS Classification ICHD-II

More IHS Resources
The International Headache Society (IHS) is the world's membership organisation for all whose

Preface to IHS-ICHD-2 website

Two years after the publication of the 2nd Edition of The International Headache Classification (ICHD-2), we are now ready to launch a web based edition. This web based version has many facilities that are not present in the printed version or a simple electronic file.
Since a Headache Classification cannot be learned by heart, it is of immense value that doctors all over the world are now able to go on the web and look after whatever question they may have regarding ICHD-2.

→ More

Table of Contents

This classification is hierarchical and you must decide how detailed you want to make your diagnosis. This can range from the first-digit level to the fourth. First one gets a rough idea about which group the patient belongs to. Is it for example 1. **Migraine** or 2. **Tension-type headache** or 3. **Cluster headache and other trigeminal autonomic cephalalgias**? Then one obtains information allowing a more detailed diagnosis. The desired detail depends on the purpose. In general practice only the first- or second-digit diagnoses are usually applied whilst in specialist practice and headache centres a diagnosis at the third- or fourth-digit levels is appropriate.

Sitemap

Consult the Sitemap to learn more about the structure of the classification and its main chapters.

→ More

IHS vs. ICD-10

To facilitate headache diagnosis in daily practice the classification provides the corresponding WHO ICD-10NA codes for each IHS code.

→ More

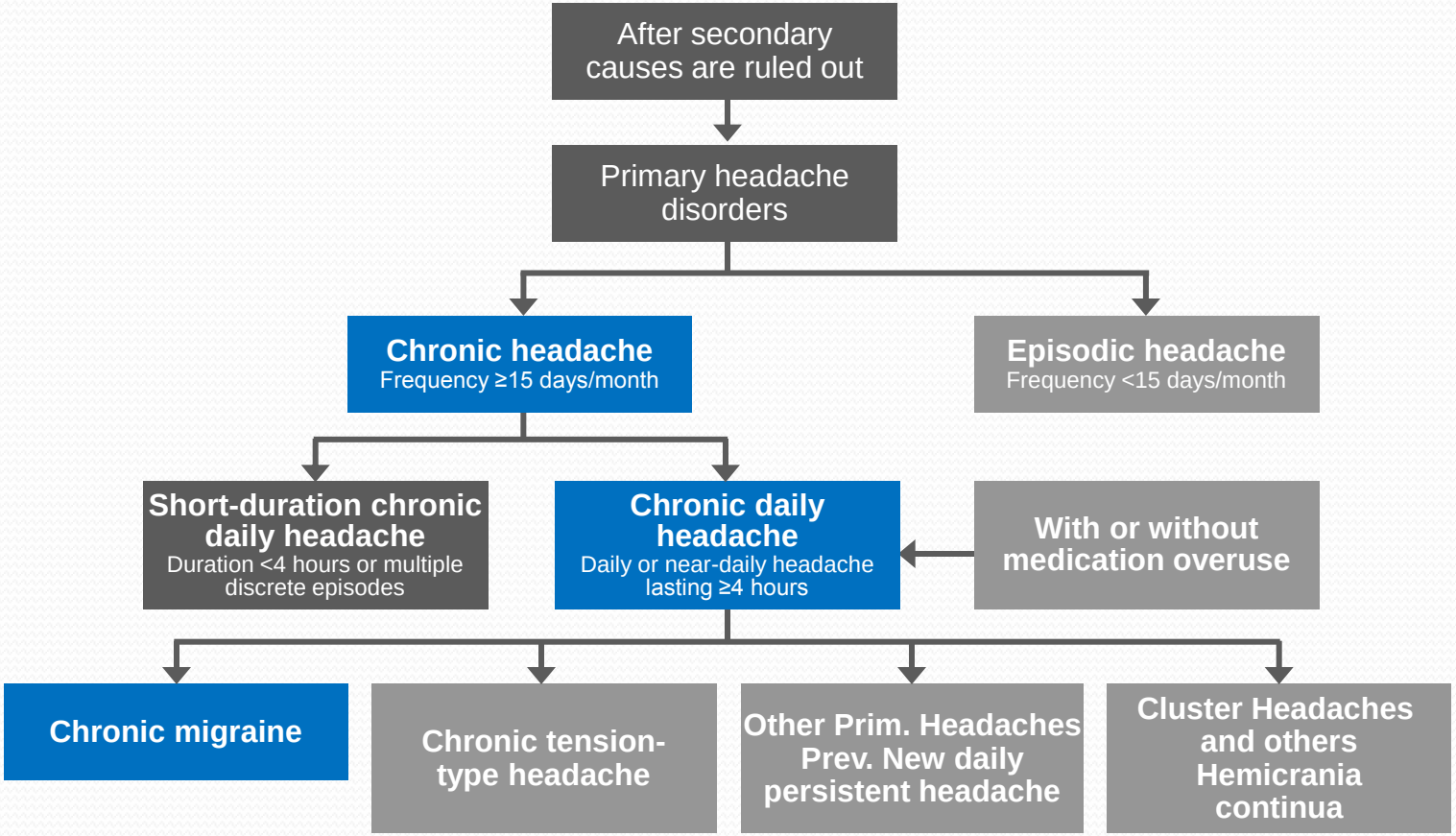
IHS Subcommittee

The Classification Subcommittee prepares and revises the International Classificatio of Headache Disorders.

→ More

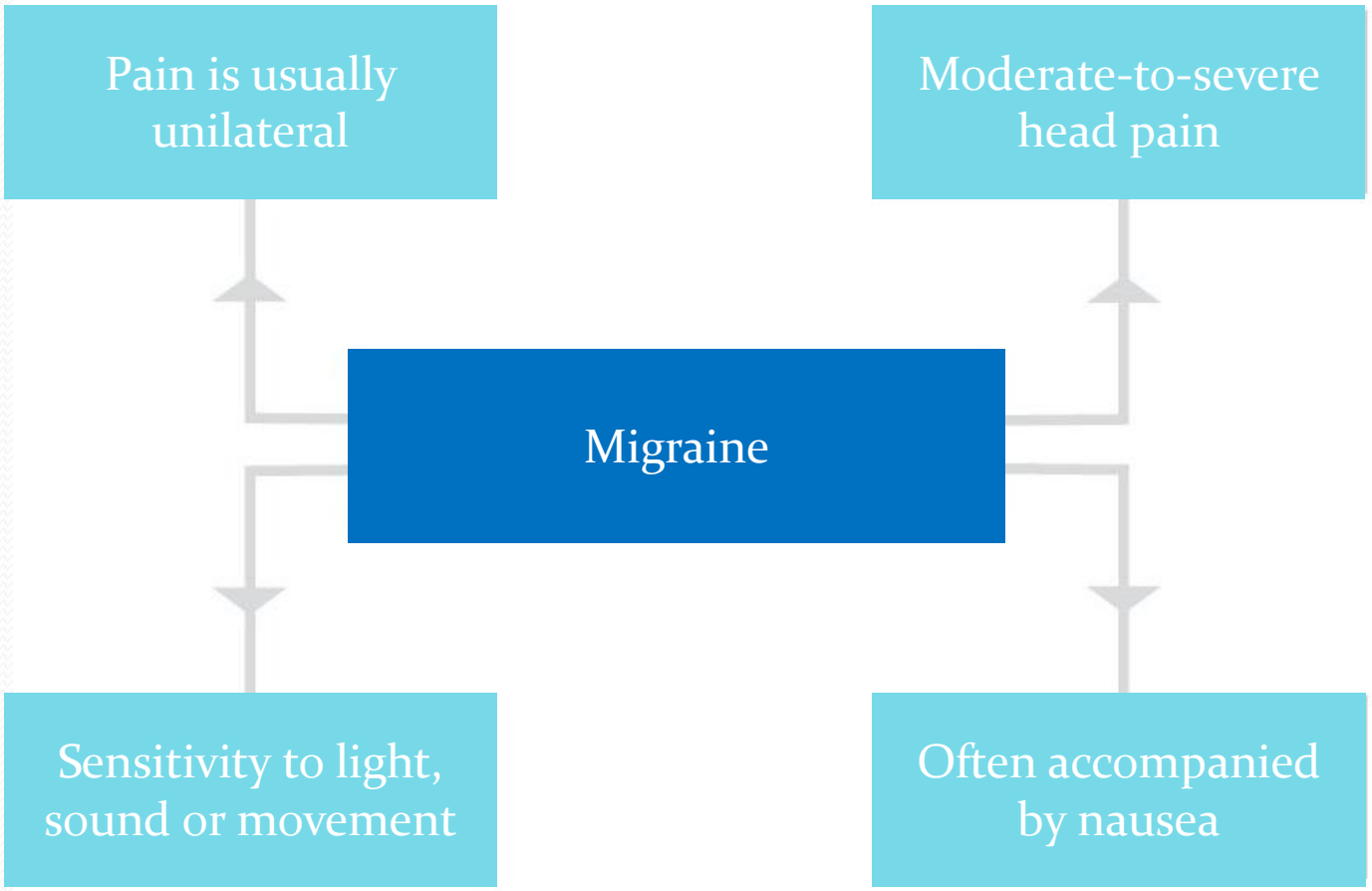
Primary headache disorders: classification according to frequency

- The primary headache disorders are broadly classified based on frequency of headache attack[1]



1. ICHD 2006 Headache Classification Committee of the International Headache Society. Olesen J *et al*. *Cephalalgia* 2006;**26**:742−746.

Migraine: characteristics[1]



1. World Health Organization (WHO) in collaboration with the European Headache Federation (EHF). *J Headache Pain* 2007;8:S1−47.

IHS	Diagnosis	ICD-10
1.1	**Migraine without aura**	**G43.0**
Previously used terms	Common migraine, hemicrania simplex	

Description:
Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia

Diagnostic criteria:

A. At least 5 attacks[1] fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[2;3;4]

C. Headache has at least two of the following characteristics:
   1. unilateral location[5;6]
   2. pulsating quality[7]
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (**eg**, walking or climbing stairs)

D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia[8]

E. Not attributed to another disorder[9]

and revises the International Classification of Headache Disorders.

→ More

Downloads

ICHD-III Beta
The International Classification of Headache Disorders, 3rd edition, beta version

→ ICHD-III Beta

Extend your electronic library with important IHS publications. All documents may be downloaded free of charge.

→ More

Cephalalgia

Cephalalgia is the official journal of the IHS. It contains original papers on all aspects of headache. The journal provides an international forum for original research papers, review articles and short communications.

→ http://cep.sagepub.com/

IHS Discussion Group

Ask questions and share information about the 2nd

1.2.1	**Typical aura with migraine headache**	**G43.10**

Description:
Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility characterise the aura which is associated with a headache fulfilling criteria for 1.1 **Migraine without aura.**

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following, but no motor weakness:
   1. fully reversible visual symptoms including positive features (**eg**, flickering lights, spots or lines) and/or negative features (**ie**, loss of vision)
   2. fully reversible sensory symptoms including positive features (**ie**, pins and needles) and/or negative features (**ie**, numbness)
   3. fully reversible dysphasic speech disturbance

C. At least two of the following:
   1. homonymous visual symptoms[1] and/or unilateral sensory symptoms
   2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
   3. each symptom lasts ≥5 and ≤60 minutes

D. Headache fulfilling criteria B-D for 1.1 **Migraine without aura** begins during the aura or follows aura within 60 minutes

E. Not attributed to another disorder[2]

Notes:

Chronic Migraine

- current practical, clinical definition are headaches of more than 4 hours ≥15 days/month and prior or current diagnosis of migraine, with or without medication overuse, > 3 months

1. Manack A *et al*. *Headache* 2009;**49**:1206–1213.

What is medication overuse headache?

- Chronic daily headache syndrome that is either a cause or consequence of a prior headache (usually migraine or tension-type headache)
- Develops through chronic overuse of acute medication taken to treat headache or other pain[1]
- Defined in the 2006 ICHD-IIR guideline as:[2]
  – Headache on ≥15 days in every month
  – Regular overuse for >3 months of acute symptomatic treatment drugs, during which time headaches have developed or worsened markedly
- Overuse of all headache medication taken on an *ad hoc* basis to relieve pain may result in medication overuse headache[3]
- Most commonly associated with regular use of simple analgesics on ≥15 days a month and/or regular use of opioids, ergots or triptans, or any combination of these, on ≥10 days a month[3]

1. Manack A *et al*. *Headache* 2009;**49**:1206−1213.
2. ICHD 2006 Headache Classification Committee of the International Headache Society. Olesen J *et al*. *Cephalalgia* 2006;**26**:742−746.
3. World Health Organization (WHO) in collaboration with the European Headache Federation (EHF). *J Headache Pain* 2007;**8**:S1−S47.

Medication overuse confounds diagnosis of chronic migraine and other chronic headache disorders

- Medication overuse confounds the diagnosis of chronic daily headache disorders, and is a significant issue[1,2]
- Not all medication-overuse patients improve after discontinuation of medication[1]
- Medication-overuse patients may be responsive to prophylactic medications after withdrawal[1]
- Medication overuse may induce the development of chronic daily headache disorders[1,2]
- Presence of medication overuse may not exclude the diagnosis of chronic migraine[3]

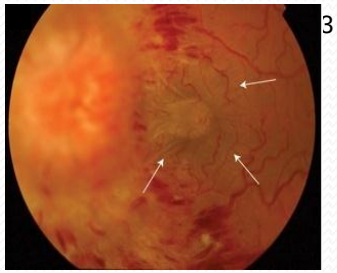
1. Headache Classification Committee. Olesen J *et al*. *Cephalalgia* 2006;**26**:742–746.
2. Lipton RB *et al*. *Neurology* 2003;**61**:154–155.
3. Manack A *et al*. *Headache* 2009;**49**:1206–1213.

Medication overuse headache is often referred to as ‘rebound’ headache.

Warning signs of secondary headache

Chronic Daily Headache ≥4 hours → Exclude secondary headache

- Systemic symptoms and signs (fever, weight loss)[1,2]
- Neurological symptoms and/or signs (pulsatile tinnitus, papilloedema)[1,2]
- Age of transformation approximately 55 years[1,2]
- Recent onset of chronic headache (<6 months)[1,2]
- Different headache pattern/worse severity of headache[1,2]
- Precipitated by valsalva or exertion; postural (e.g. worse in upright or recumbent position)[1,2]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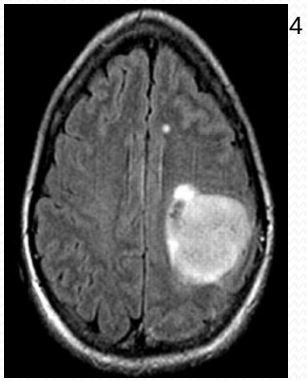

4

1. Dodick D. *N Engl J Med* 2006;**354**:158–165.
2. Bigal ME *et al. J Headache Pain* 2007;**8**:263–272.
3. Pandya VB *et al*. *MJA* 2008;**189**:413.
4. Cha S. *Am J Neuroradiol* 2006:**27**:475–487.

SNOOP4: Ruling Out Secondary Causes of Headache in Migraine

- S ystemic symptoms and signs
- N eurologic symptoms or signs
- O nset: peak at onset or <1 minute
- O lder: after age 50 years
- P revious headache: pattern change
- P ostural, positional aggravation
- P recipitated by valsalva, exertion etc
- P apilloedema

Silberstein SD, Lipton RB in:Silberstein SD et al. eds. Wolff's Headache and Other Head Pain. 8th ed. New York: Oxford University Press; 2008;315-377

Add a snoop4 shortcut key

- Systemic symp … Neurologic symp … Onset <1min … Older > 50 … Prev HA pattern change … Postural, positional aggravation … Precipitated by valsalva … Papilloedema …

Botulinum Toxin Type A

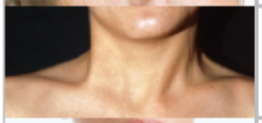
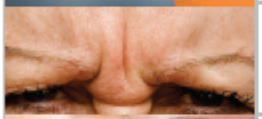
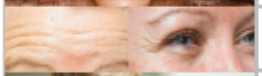
- Injector since 2004
- Safe
- Actions
- Side Effects
- Bruxism /Facial Shaping/Cosmetic ->Migraine 2005
- Joint program using physiotherapy improves effectiveness of program
- Official validation of use of Botulinum Toxin Type A with the publication of the PREEMPT Clinical Program – RCT - the only proven prophylatic tx for CM

Botulinum Toxin Type A Onabotulinumtoxin A or Botox®

- is a natural, purified protein that relaxes muscles and inhibits sweat glands
- A simple and quick, minimally invasive non-surgical treatment
- is the only product of its kind with a proven 20-year safety record and effective use in millions of patients worldwide & 20 YEARS of data and experience (Ref: Naumann M et al. Curr Med Res Opin 2004)
- 7 toxin serotypes A to G
- Not interchangeable 3 Aug 2009
- Most common side effect is tenderness or bruising at the site of injection
- Less frequent side effects can include headache, temporary eyelid droop and nausea
- BOTOX® is currently available in approximately 80 countries. http://www.allergan.com/products/neurosciences/index.htm
- 20 MILLION procedures (Refs: Naumann M et al. Curr Med Res Opin 2004; American Society of Plastic Surgeons, 2009; Plastic Surgery Reseach, 2009)

BOTOX® approved indications[1]

Botulinum Toxin Type A

	Indication	Date of approval in Australia/New Zealand
	Focal spasticity in adults	2003 (ANZ)
	Strabismus in children (>2years) and adults	2005/1991
	Focal spacticity of upper & lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients > 2 years	2007/2008
	Blepharospasm	1993/1991
	Cervical dystonia	2000/1993
	Spasmodic dysphonia	2005/(not approved in New Zealand)
	Severe primary hyperhidrosis of the axillae	2001 (ANZ)
	Glabellar lines	2002/2001
	Forehead lines, Crow's feet	2007/2006
	Chronic migrane	2011 (ANZ)
	Juvenile cerebral palsy	1998/2001

References: 1. BOTOX® Approved Product Information Allergan Australia.

Botulinum Toxin

- It is the most acutely toxic substance known, with a median lethal dose of about 1 ng/kg when introduced intravenously[1] and 3 ng/kg when inhaled.[2] This means, depending on the method of introduction into the body, a mere 90–270 nanograms of botulinum toxin could be enough to kill an average 90-kg (200-lb) person, and four kg of the toxin, if evenly distributed, would be more than enough to kill the entire human population of the world.

- ^1[a] [b] Arnon, Stephen S.; Schechter R, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Hauer J, Layton M, Lillibridge S, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Swerdlow DL, Tonat K; Working Group on Civilian Biodefense. (21 February 2001). "Botulinum Toxin as a Biological Weapon: Medical and Public Health Management" (PDF, 0.5 MB). *Journal of the American Medical Association*

- ^ "Emergency preparedness: Botulism". *Physician Information Link*. Anne Arundel County Department of Health. June 17, 2004. Retrieved 2010-07-14.

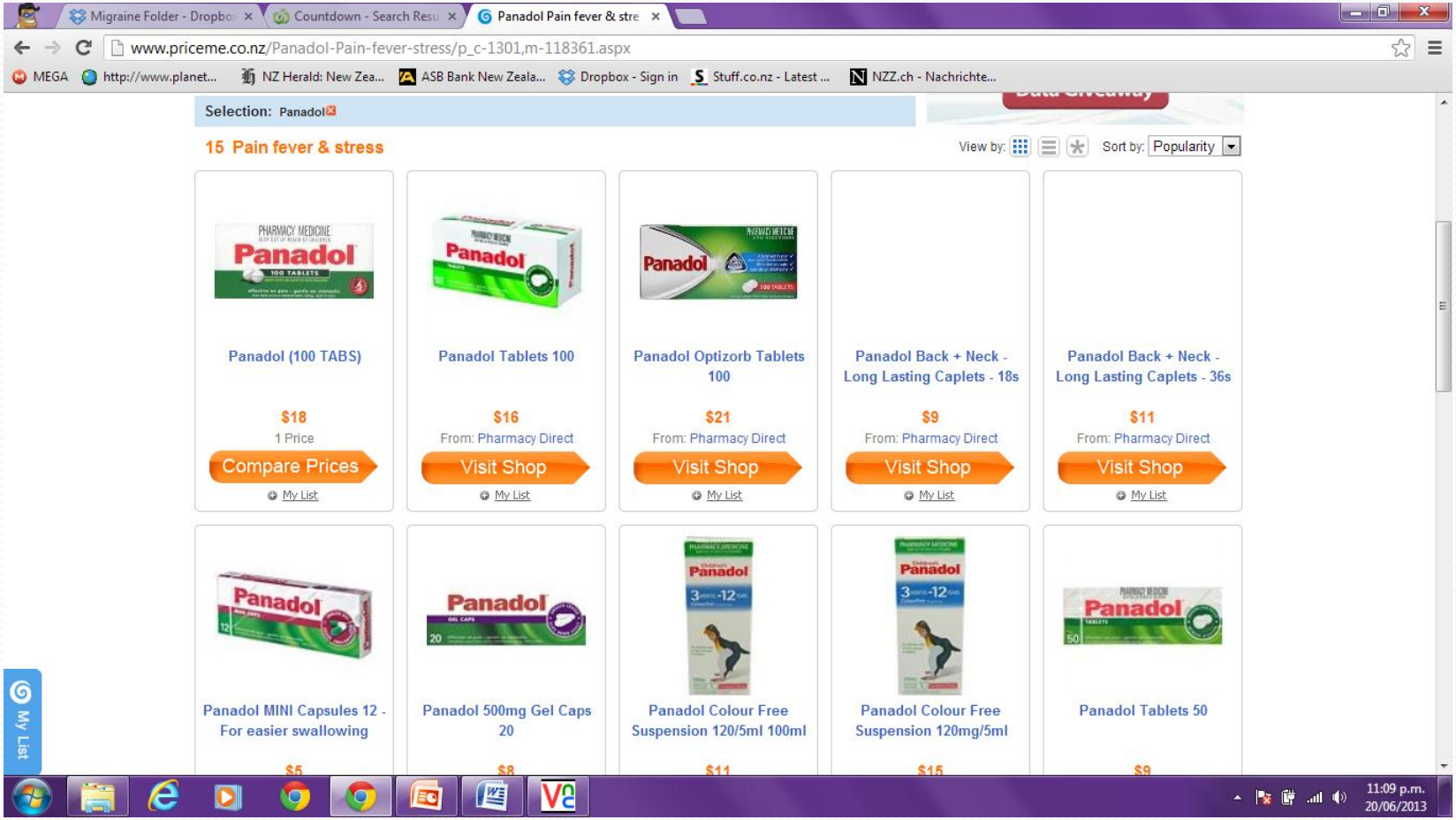
- 1 microgram = 1000 nanograms
- 1 milligram = 1000 micrograms
- 1 gram = 1000 milligrams

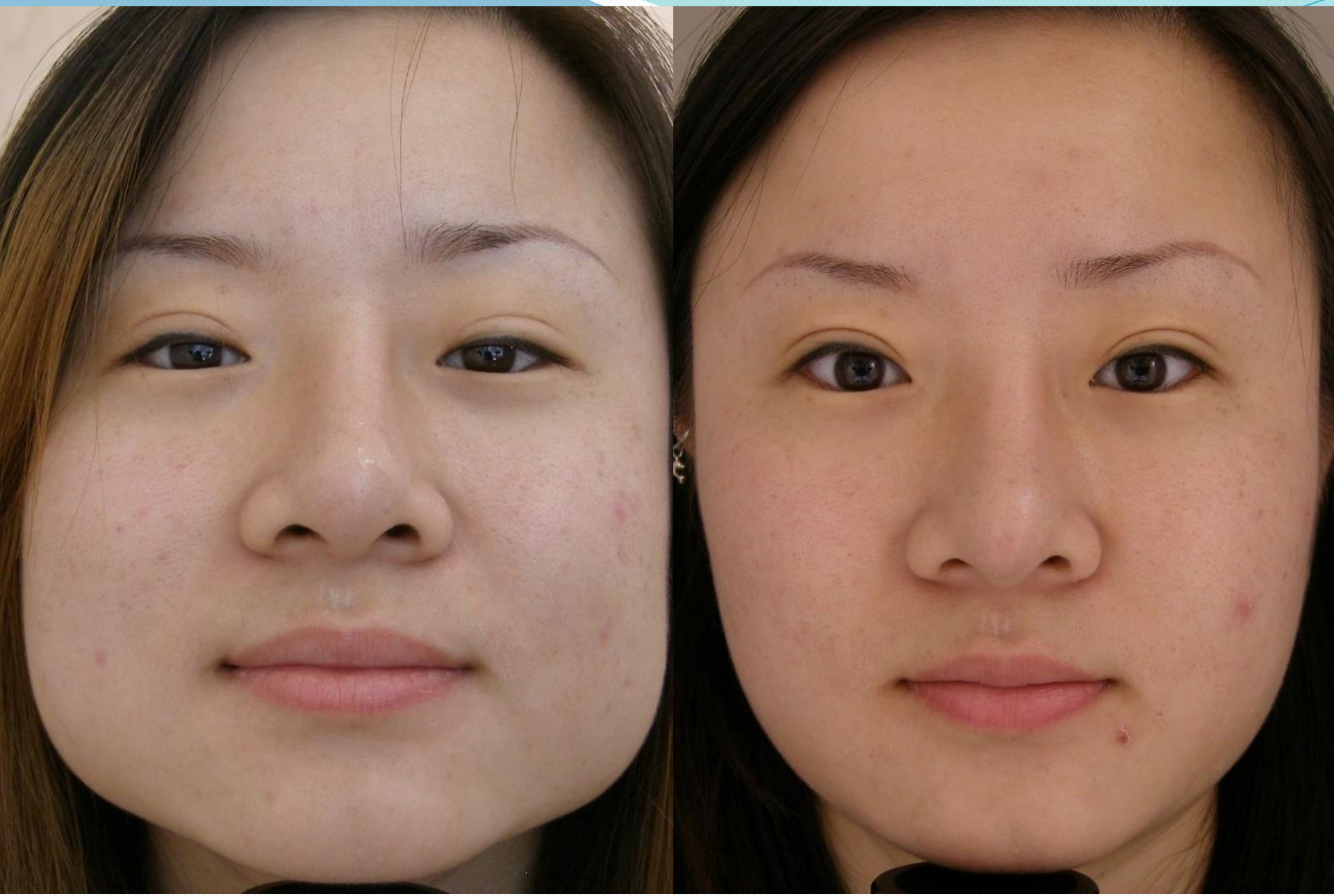
SUBSTANCE	ANIMAL/ROUTE	LD50	LD50 g/kg	Reference
Botulinum toxin (Botox)	human, oral, injection, inhalation	1 ng/kg approx 20.8units (estimated)	0.000000001	Nigam PK et al Botulinum Toxin Indian J Dermatol 2010 Jan-Mar;55(1) 8-14
Paracetamol (acetaminophen)	rat, oral	1,944 mg/kg	1.944	[15]
Coumarin (benzopyrone, from Cinnamomum aromaticum and other plants)	rat, oral	293 mg/kg	0.293	[19]
Aspirin (acetylsalicylic acid)	rat, oral	200 mg/kg	0.2	[20]
Caffeine	rat, oral	192 mg/kg	0.192	[21]
Venom of the Inland Taipan (Australian snake)	rat, subcutaneous	25 µg/kg	0.000025	[41]
Sarin	mouse, subcutaneous injection	17.23 µg/kg (estimated)	0.0000172	[44]
Bisoprolol	mouse, oral	100 mg/kg	0.1	[24]

How safe is Botox?

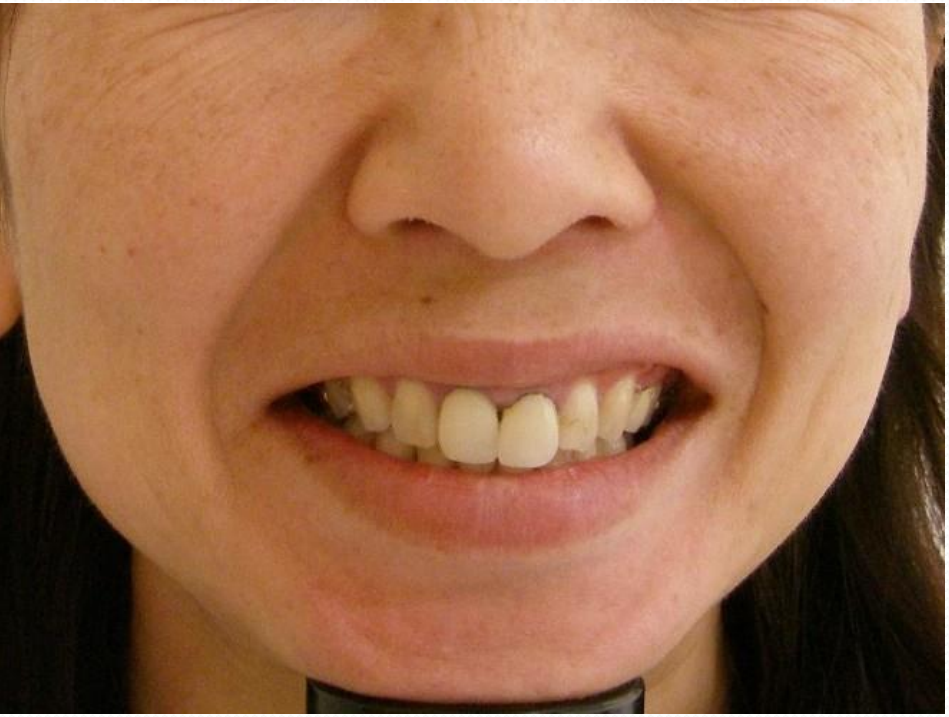
- 1nanogram of Botox is approx 20units
- Average 70kg man needs 1,400 units of Botox to reach a lethal dose = $35,000 of Botox in a 3 month period
- Average dose for cosmetic area is 20units
- Average dose for Chronic Migraine Patients is 130units

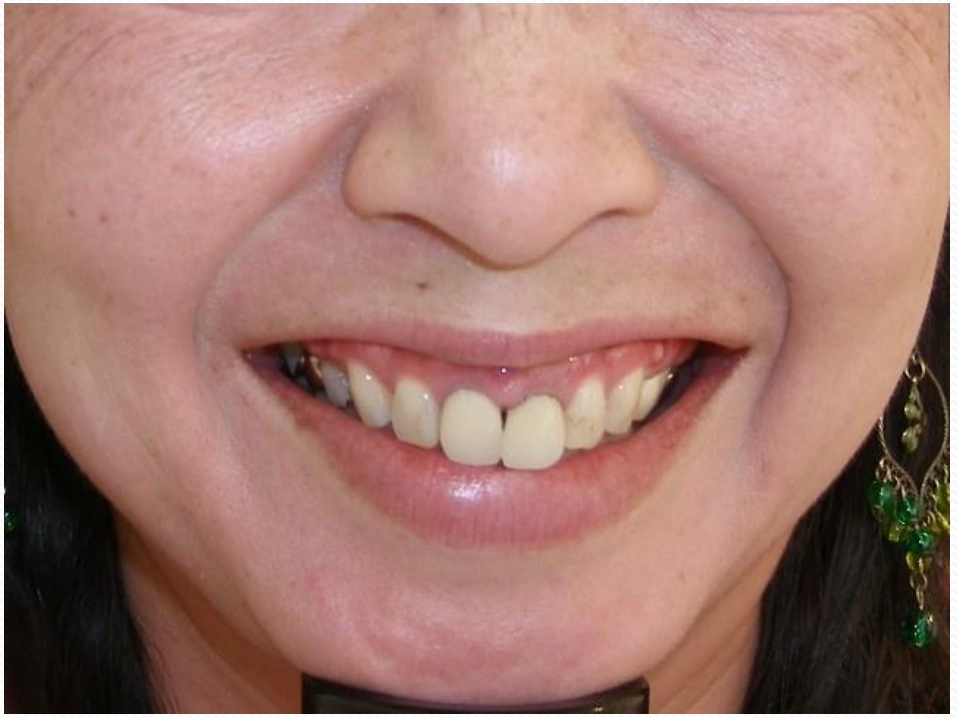
Irreversible hepatotoxicity occurs with less than 15g ie 30tabs of over the counter paracetamol



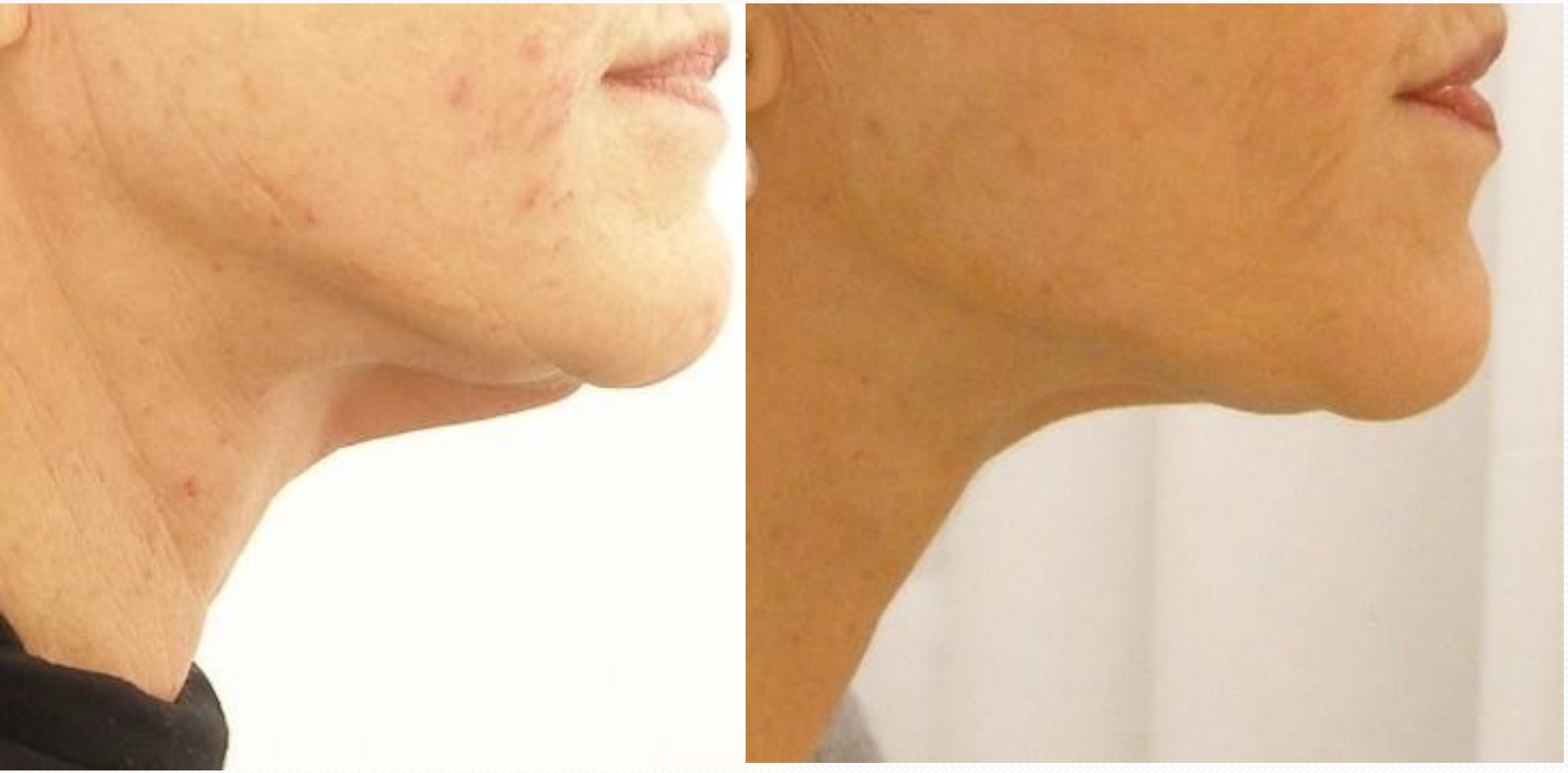


Botulinum Toxin Type A facial shaping

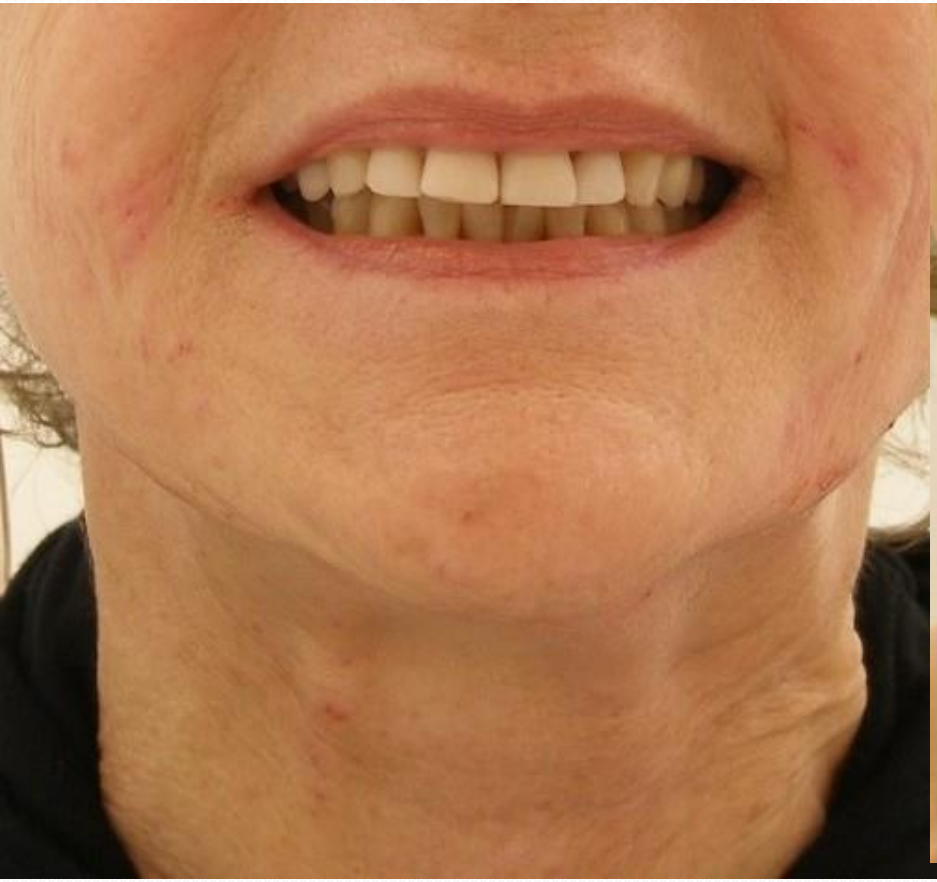


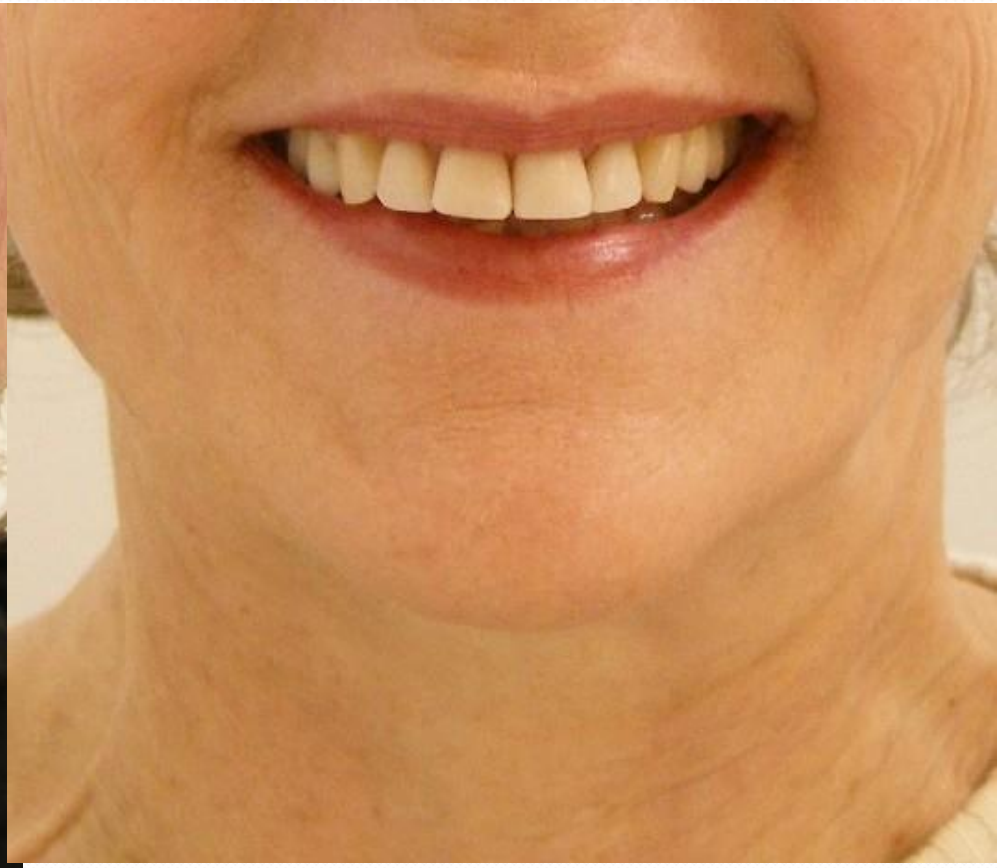


Botulinum Toxin Type A correcting your smile



2 weeks after Botulinum Toxin Type A lower facial lift





2 week after Botulinum Toxin Type A lower facial lift (both photos are of the patient doing the same action - grimacing)

What do I do?

- All patients booked into the Migraine Clinic are sent questionnaires which they must return before a booking is made
- Headache diary
- HIT-6
- Becks Depression Score
- Migraine Definition
- Chronic Migraine Definition
- Outline of cost

(VERSION 1.1)

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

IMPACT TEST™

1 When you have headaches, how often is the pain severe?

Never | Rarely | Sometimes | Very Often | Always

2 How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never | Rarely | Sometimes | Very Often | Always

3 When you have a headache, how often do you wish you could lie down?

Never | Rarely | Sometimes | Very Often | Always

4 In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never | Rarely | Sometimes | Very Often | Always

5 In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never | Rarely | Sometimes | Very Often | Always

6 In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never | Rarely | Sometimes | Very Often | Always

COLUMN 1 (6 points each)	+	COLUMN 2 (8 points each)	+	COLUMN 3 (10 points each)	+	COLUMN 4 (11 points each)	+	COLUMN 5 (13 points each)

To score, add points for answers in each column.

Please share your HIT-6 results with your doctor.

Total Score

Higher scores indicate greater impact on your life.

Score range is 36–78.

Headache Impact Test - 6

HEADACHE IMPACT TEST™

What Does Your Score Mean?

If You Scored 60 or More

Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in your life, like family, work, school or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 56 – 59

Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 50 – 55

Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.

Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

If You Scored 49 or Less

Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to continue to track how your headaches affect your life.

BECKS DEPRESSION INVENTORY FOR MIGRAINE PATIENTS

sapphire
appearance **medicine** clinic

Name: _____ Age: _____ Sex: ___ Occupation: _____ Marital Status: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group carefully, and then pick out **ONE** statement that best describes the way you are feeling during the **past 2 weeks, including today**. Please write the number you have chosen in the square provided. If several statements in a group seem to apply equally well, circle the highest number for that group. Be sure you do not choose more than one.

1. ☐
   0 I do not feel sad.
   1 I feel sad.
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad and unhappy that I can't stand it.

2. ☐
   0 I am not particularly discouraged about my future.
   1 I feel discouraged towards my future.
   2 I feel I have nothing to look forward to.
   3 I feel the future is hopeless and that things cannot improve.

3. ☐
   0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.

4. ☐
   0 I get as much satisfaction out of the things I used to.
   1 I don't enjoy things the way I used to.

Definition of Success

- 50% reduction in frequency of headaches/migraines
- 50% reduction in acute medication
- Each visit, HIT-6 and Becks Depression Inventory is compared

Case Presentation

- MA 36y/o female on invalids benefit
- Aged 16 first migraine after seizure
- Recent MRI and CT scan, no intracranial lesion
- Headaches more than 4 hours per day, every day for 15 years.
- Migraines three days per week
- Pethidine inj & tablets, Nortriptyline, Brufen, Codiene, Paracetamol.
- Injected with Botox on 20th June 2013
- Txt today

Case Presentation

- TL 28y/o female, flight attendant.
- Aged 8 first migraine with aura
- Headaches more than 4 hours per day, 16 days a month for years.
- Migraines three days per month
- Brufen, Codeine, Buccastem, Imigran
- Injected with Botox on 4th April 2013
- No headaches since then.

Don’t forget…

- It must not be forgotten however that migraine headache is a phenomenon that has other major contributing factors that contribute to its aetiology;
- these being a neurovascular component,
- a hormonal component,
- and finally the hypersensitivity and or allergenic component [Watson, 2003 #1].

Management of migraine and chronic migraine using Botulinum Toxin Type A

Non-pharmacological treatment: trigger avoidance

- As a first step in the management of migraine, many patients will try to identify their migraine triggers and use avoidance as a treatment strategy[1]
- If this is not effective, patients may try, and health professionals may recommend, alternative or approaches to headache care[2]

1. Migraine in primary care advisors (MIPCA). Treatment guidelines for migraine. 2006. www.mipca.org.uk/guidelines_mig.htm. Accessed May 2010.
2. Vickers AJ *et al*. *Health Technol Assess* 2004;**8**:1−35.

Pharmacological treatment options

- Approaches to the pharmacological management of migraine can be either acute (relief) or prophylactic (preventive), depending on the frequency of migraine headache
- The EFNS / BASH guidelines are as follows

Acute Treatment	Prophylactic Treatment
■ Medication taken during a migraine attack to relieve symptoms	■ Medication used to reduce the number of attacks when acute therapy, used appropriately, gives inadequate control of symptoms[2]
■ Used when the frequency of the attacks is <2/month[1]	■ Used when the frequency of attacks is ≥2/month[1]

1. Evers S *et al*. *Eur J Neurol* 2009;**16**:968–981.
2. BASH Guidelines 2007. http://216.25.88.43/upload/NS_BASH/BASH_guidelines_2007.pdf Accessed May 2010.

Chronic migraine: principles of management

- Accurate diagnosis[1]
- Identification and minimisation/elimination of trigger and aggravating factors[1,2]
- Identification and management of coexistent, comorbid disorders, and other factors that influence prognosis[1,2]
- Thorough understanding of patient's current medication use[2]
- Establishment of treatment plan[1,2]
  - Non-pharmacological
  - Pharmacological (acute and preventive); establish limits on acute and rescue therapy
- Assessment and monitoring of level of headache-related disability[3]

1. Vargas BB *et al*. *Neurol Clin* 2009;**27**:467–479.
2. Dodick DW. *N Engl J Med* 2006;**354**:158–165.
3. Silberstein SD *et al*., eds. *Headache in Clinical Practice*. 2nd ed. London: Martin Dunitz; 2002:11–19.

Establishing realistic goals is key for chronic migraine management

- The main goals for treatment of chronic migraine are to decrease disability and improve health-related quality of life (HRQoL)[1]
- Goals include improvement in headache burden by reducing:[1]
  - Headache days
  - Headache duration
  - Headache intensity and severity
- Benefits occur over time and cannot be expected immediately[1]

1. Dodick DW, Silberstein SD. *Pract Neurol* 2007;**7**:383–393.

Prophylaxis of chronic migraine: the unique role of Botulinum toxin type A

- Prophylactic treatment is recommended in those patients who experience ≥2 migraines/month[1]
- Chronic migraine is classified by the ICHD as ≥15 headache days/month for >3 months, of which ≥8 are migrainous[2]
- Patients with chronic migraine are therefore candidates for migraine prophylaxis
- Few preventive treatments have been investigated for patients with chronic migraine[3]
- BOTOX® is currently the only treatment specifically licensed by regulators for prophylaxis of headache in this population[4]

1. Evers S *et al*. *Eur J Neurol* 2009;**16**:968–981.
2. ICHD 2006 Headache Classification Committee of the International Headache Society. Olesen J *et al*. *Cephalalgia* 2006;**26**:742−746.
3. Aurora AK *et al.* Poster presented at *14th International Headache Congress*, September 10–13, 2009, Philadelphia, PA, USA.
4. BOTOX® UK Summary of Product Characteristics. Allergan Ltd.

Injection Paradigm

Headache
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Research Submissions

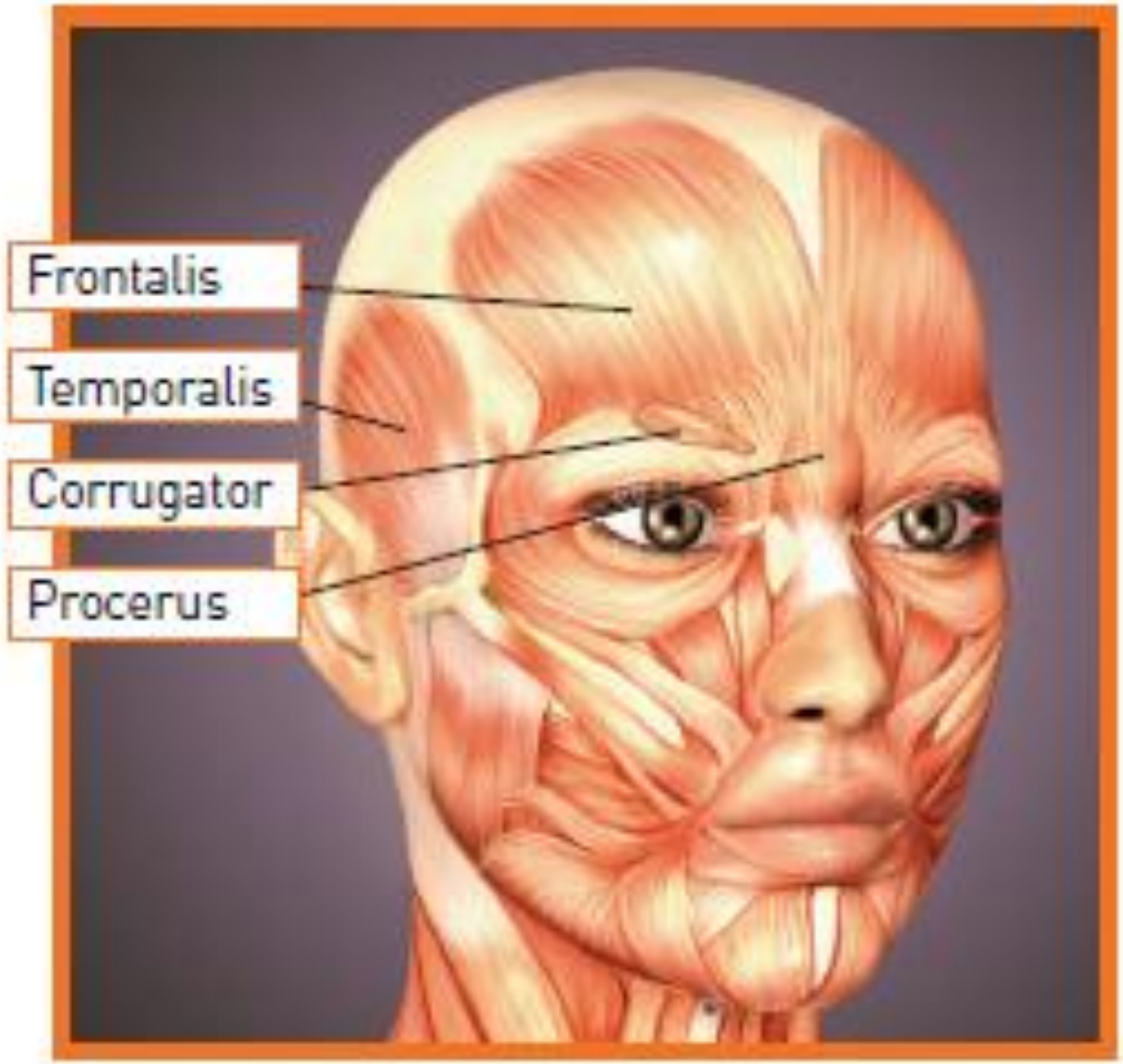
Method of Injection of OnabotulinumtoxinA for Chronic Migraine: A Safe, Well-Tolerated, and Effective Treatment Paradigm Based on the PREEMPT Clinical Program

Andrew Blumenfeld, MD; Stephen D. Silberstein, MD, FACP; David W. Dodick, MD; Sheena K. Aurora, MD; Catherine C. Turkel, PharmD, PhD; William J. Binder, MD, FACS

Chronic migraine (CM) is a prevalent and disabling neurological disorder. Few prophylactic treatments for CM have been investigated. OnabotulinumtoxinA, which inhibits the release of nociceptive mediators, such as glutamate, substance P, and calcitonin gene-related peptide, has been evaluated in randomized, placebo-controlled studies for the preventive treatment of a variety of headache disorders, including CM. These studies have yielded insight into appropriate patient selection, injection sites, dosages, and technique. Initial approaches used a set of fixed sites for the pericranial injections. However, the treatment approach evolved to include other sites that corresponded to the location of pain and tenderness in the individual patient in addition to the fixed sites. The Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) injection paradigm uses both fixed and follow-the-pain sites, with additional specific follow-the-pain sites considered depending on individual symptoms. The PREEMPT paradigm for injecting onabotulinumtoxinA has been shown to be safe, well-tolerated, and effective in well-designed, controlled clinical trials and is the evidence-based approach recommended to optimize clinical outcomes for patients with CM.

- The PREEMPT clinical programme has established a successful treatment paradigm.
- Although muscle groups injected in PREEMPT were the same as those injected in the preceding phase 2 trials, there were revisions.

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418


Frontalis
Temporalis
Corrugator
Procerus

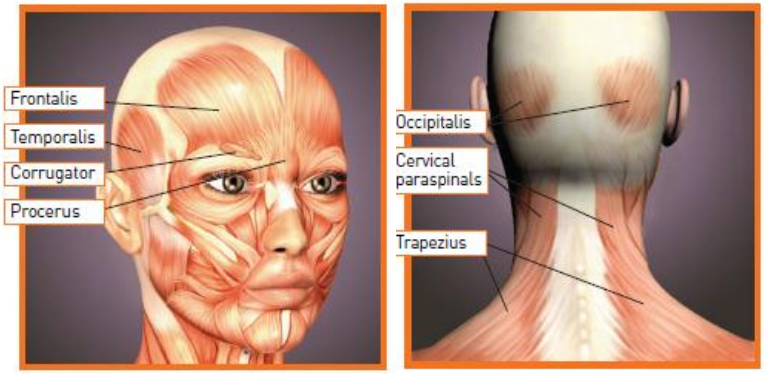
Injection Paradigm

AU/0056/2011

(Fixed-site, Fixed-dose & Modified Follow-the-Pain Models)

Fixed-site, Fixed-dose

- 155 U of BOTOX® (botulinum toxin, type A)
- 31 fixed-sites with fixed-dose (5 U/injection site)
- Injections across 7 specific head/neck muscle areas



Modified Follow-the-Pain strategy

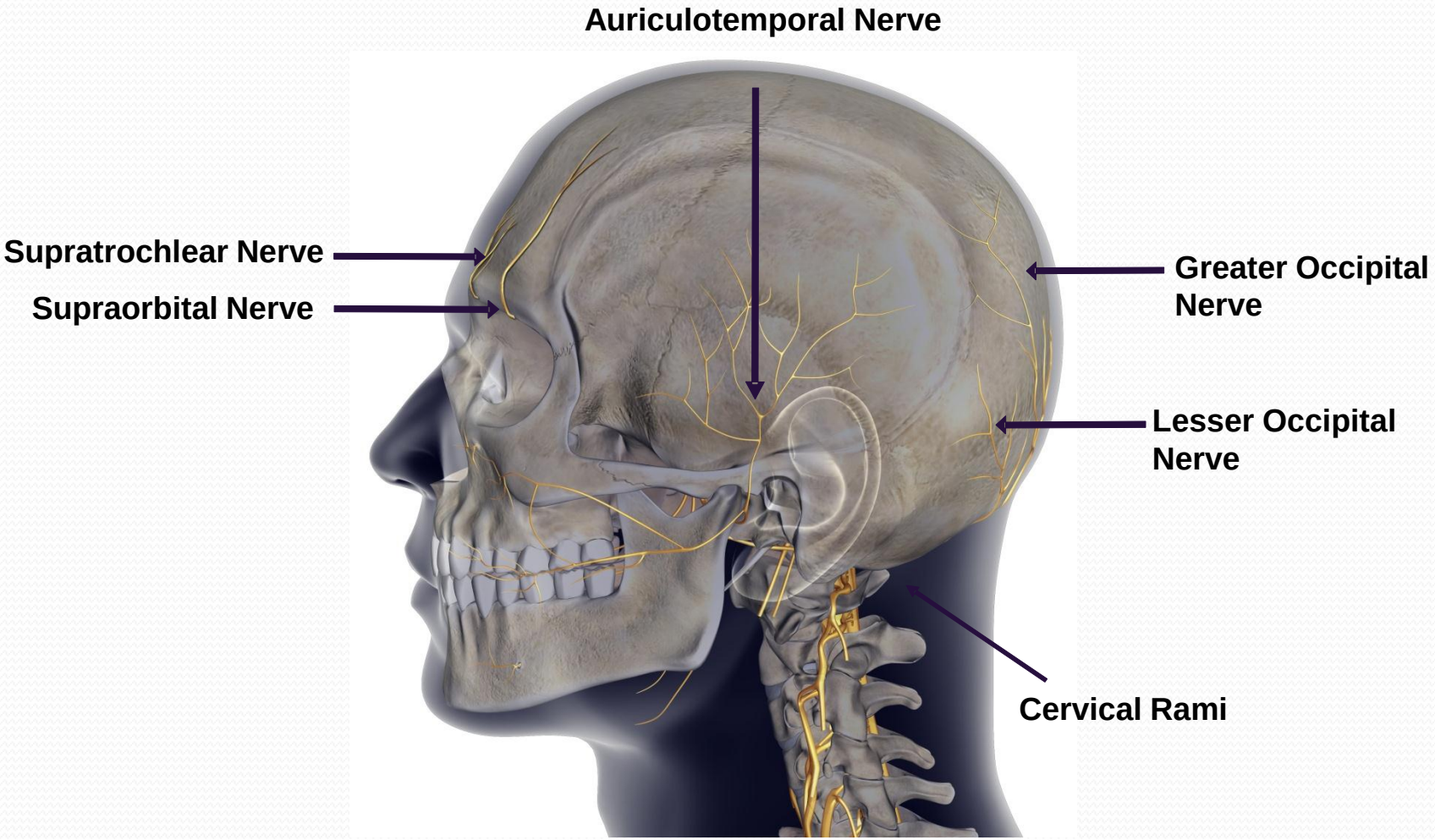
- Up to 40 U of additional BOTOX®
- 8 additional sites (5 U/injection site)
- Maximum total dose of 195 U
- The decision to inject additional BOTOX® is left to the judgment of the injecting physician

Dosing

- For each injection site, the injection volume will be 0.1 mL (5 U)
- Each muscle has a fixed:
  - Total dose
  - Number of injection sites
  - Location of injection sites

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

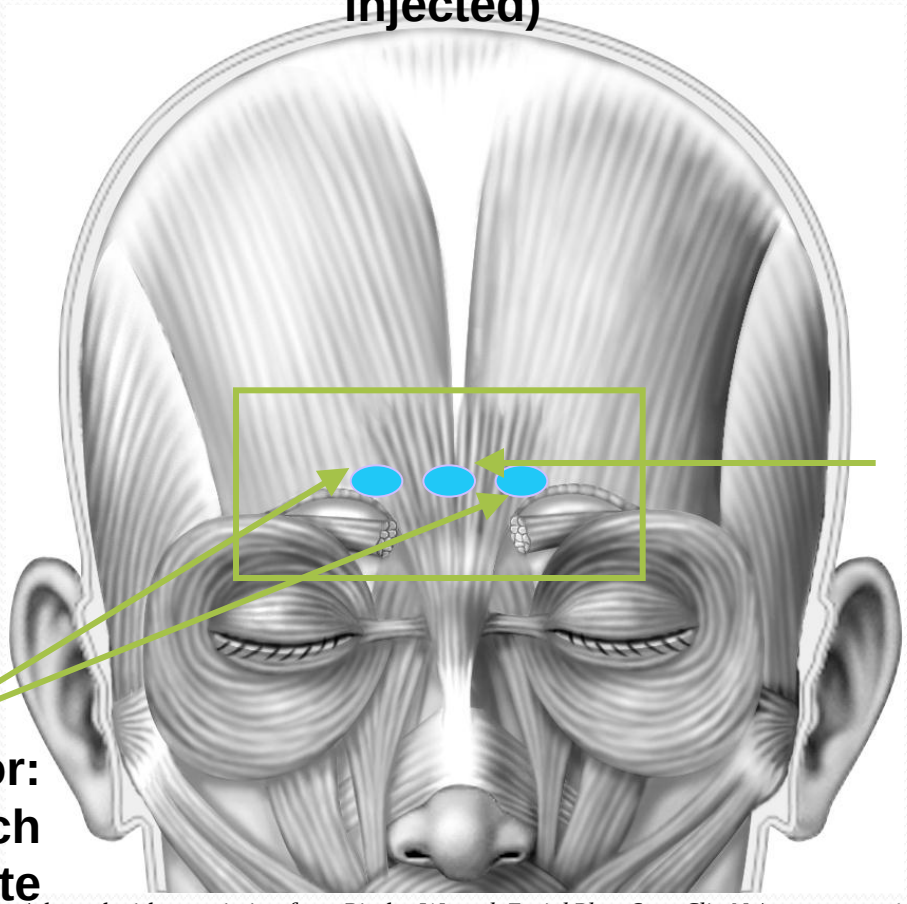
Anatomical Injection Sites Follow Distributions & Areas Innervated by the Trigeminal Sensory System

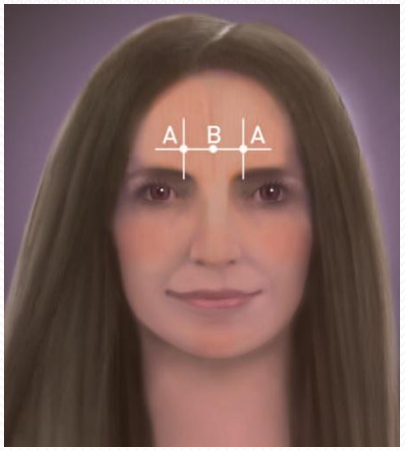


Schuenke M *et a.*, eds. *Theime Atlas of Anatomy: Head and Neuroanatomy*. Stuttgart: Thieme; 2010.

Injection Sites: Corrugator & Procerus

5 U BOTOX® per injection (0.1 mL injected)





Procerus: 5 U at site

Corrugator: 5 U at each site

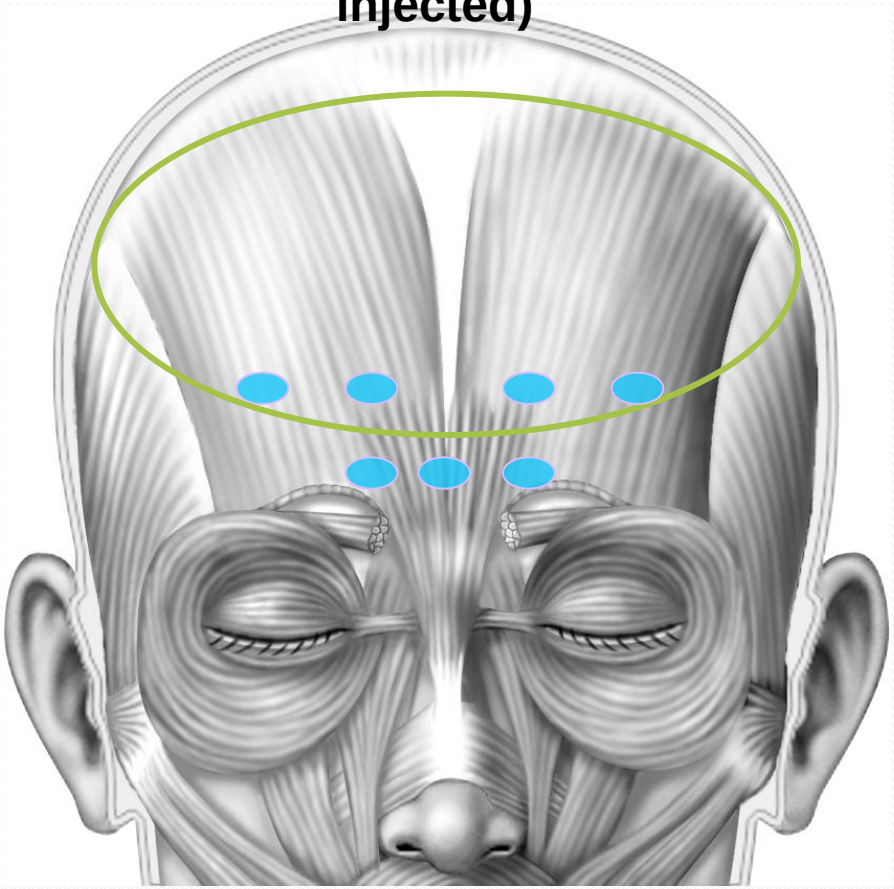
Adapted with permission from Binder W *et al. Facial Plast Surg Clin N Am*. 2003;11:465-475.

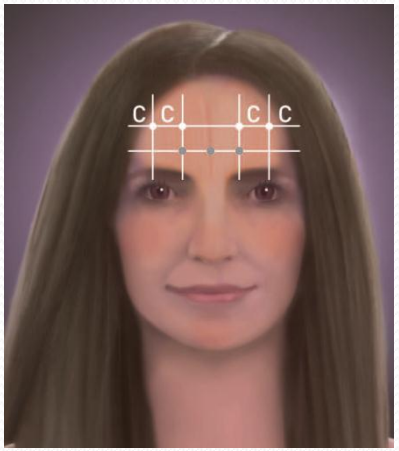
Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

Injection Site: Frontalis Region

AU/0056/2011

5 U BOTOX® per injection (0.1 mL injected)



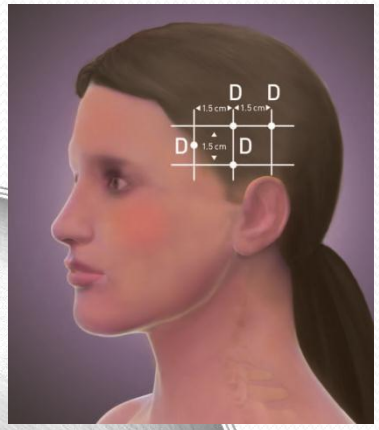


Adapted with permission from Binder W *et al. Facial Plast Surg Clin N Am*. 2003;11:465-475.

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

Injection Sites: Temporalis

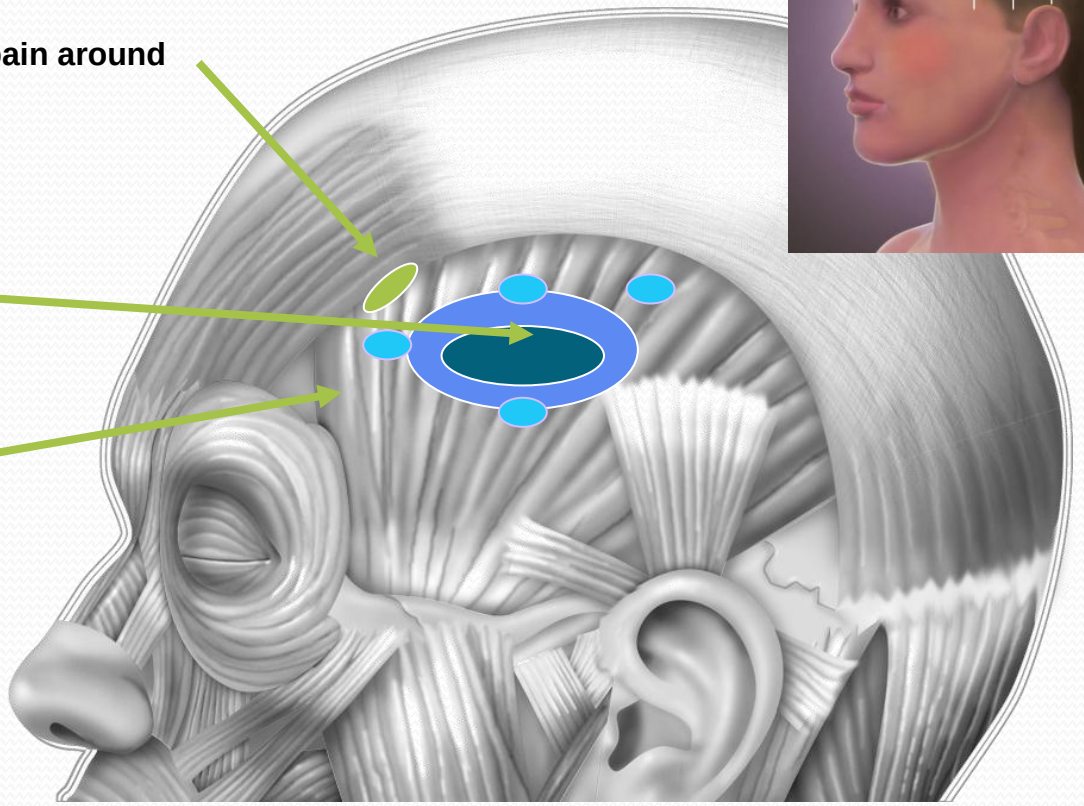
5 U BOTOX® per injection (0.1 mL injected)



Patients may specifically have pain around the temporal artery

Having the patient clench teeth will produce a palpable anterior bulge to the temporalis muscle, directing the anterior injection site

An additional 2 optional follow-the-pain sites may be injected, depending on the patient's self report of pain or tenderness

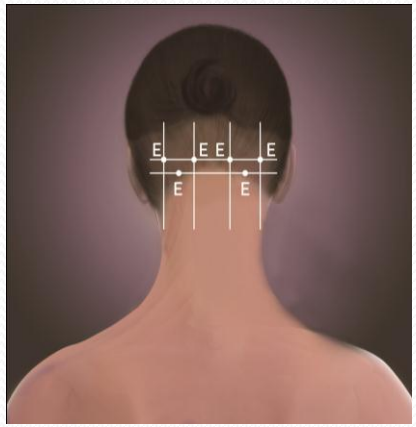


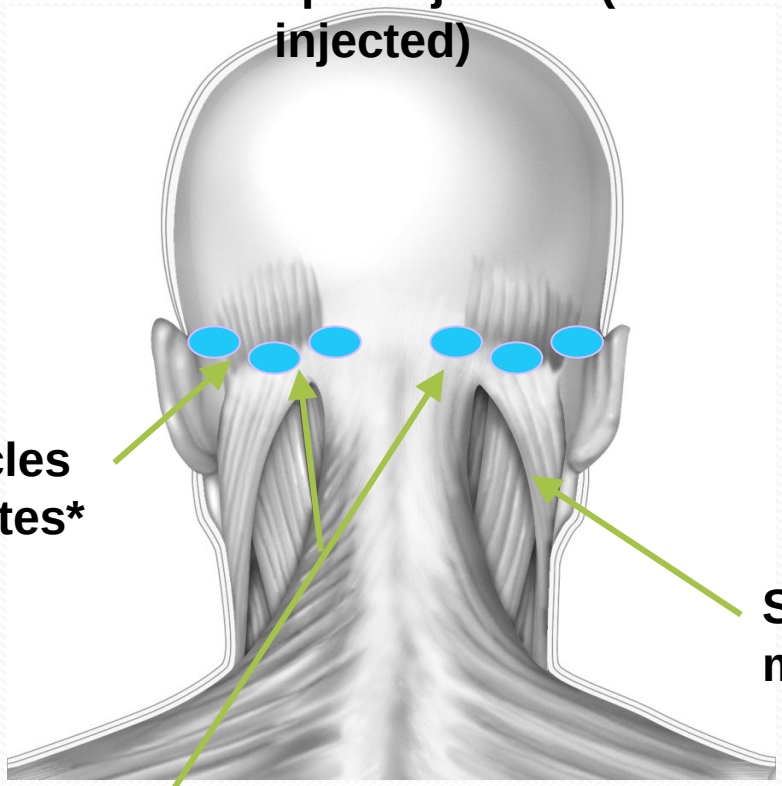
Adapted with permission from Binder W *et al. Facial Plast Surg Clin N Am*. 2003;11:465-475.

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

Injection Site: Occipitalis

5 U BOTOX® per injection (0.1 mL injected)





Occipitalis muscles and injection sites*

Sternocleidomastoid muscle

Nuchal ridge

Adapted with permission from Binder W *et al. Facial Plast Surg Clin N Am*. 2003;11:465-475.

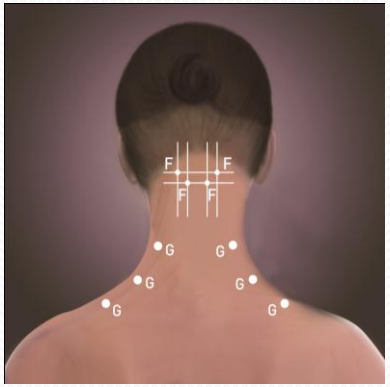
*An additional 2 injections of 5 U can be distributed between the right and left occipitalis muscles in the areas identified as having maximal pain and tenderness.

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

Injection Sites: Cervical Paraspinal & Trapezius

AU/0056/2011

5 U BOTOX® per injection (0.1 mL injected)



Adapted with permission from Binder W *et al. Facial Plast Surg Clin N Am*. 2003;11:465-475.

*No additional injections in the cervical paraspinal muscles.

†Up to an additional 4 injections each of 5 U may be distributed between the right and left trapezius muscles based on pain and maximal tenderness. The infero-medial portions of the trapezius muscle should be avoided to limit the possibility of neck weakness.

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

Injection Paradigm: Required Dose Using a Fixed-Site, Fixed-Dose Paradigm

AU/0056/2011

Order	Muscle	Number of Units (U)
A	Corrugator	10 (5 each side)
B	Procerus	5
C	Frontalis	20 (10 each side)
D	Temporalis	40 (20 each side)
E	Occipitalis	30 (15 each side)
F	Cervical paraspinal	20 (10 each side)
G	Trapezius	30 (15 each side)
Total number of units (U)		**155**

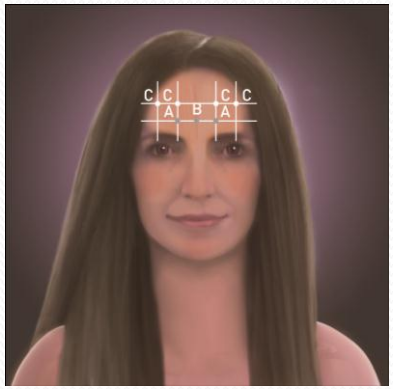
Dosing and results in these studies are specific to the formulation of BOTOX® manufactured by Allergan, BOTOX® is not interchangeable with other botulinum toxin products and cannot be converted using a dose ratio.

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

Order of Injection & Patient Position: Fixed-Site Fixed-Dose

The anatomic injection sites follow distributions & areas innervated by the trigeminal nerve complex

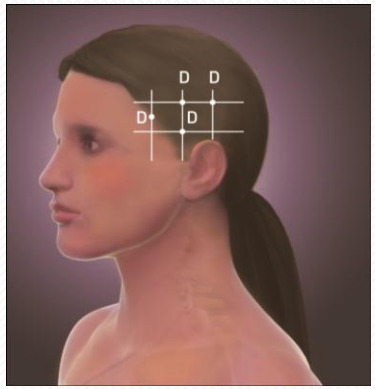
Supine



A. Corrugator: 5 U each side

B. Procerus: 5 U (one site)

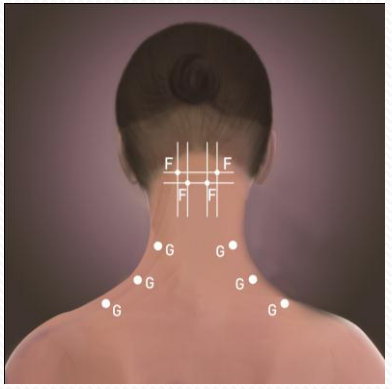
C. Frontalis: 10 U each side



D. Temporalis: 20 U each side

Sitting

E. Occipitalis: 15 U each side



F. Cervical paraspinal: 10 U each side

G. Trapezius: 15 U each side

AU/0056/2011

0.1 mL = 5 U/site

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

Dosing for Chronic Migraine Using the PREEMPT Follow-the-Pain Injection Paradigm

Order	Muscle	Number of Units (U)*		Additional Units (U), if necessary
A	Corrugator†	10 (5 each side)		**NA**
B	Procerus	5		**NA**
C	Frontalis†	20 (10 each side)		**NA**
D	Temporalis†	40 (20 each side)	**+**	**10 (up to 2 sites)**
E	Occipitalis†	30 (15 each side)	**+**	**10 (up to 2 sites)**
F	Cervical paraspinal†	20 (10 each side)		**NA**
G	Trapezius†	30 (15 each side)	**+**	**20 (up to 4 sites)**
Total number of units (U)		**155**	**to**	**195**

Dosing and results in these studies are specific to the formulation of BOTOX® manufactured by Allergan, Inc. (Irvine, CA).
The Allergan, Inc., formulation is not interchangeable with other botulinum toxin products and cannot be converted using a dose ratio.

*Each IM injection site = 0.1 mL = 5 U BOTOX.
†Dose distributed bilaterally for the minimum 155 U dosing.

NA = no additional

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

Order of Injection & Patient Position: Follow-the-Pain

AU/0056/2011

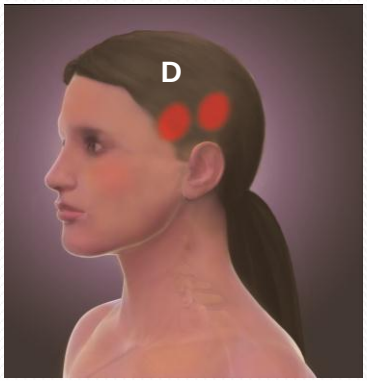
The anatomic injection sites follow distributions and areas innervated by the trigeminal nerve complex

Supine

A. Corrugator: no additional

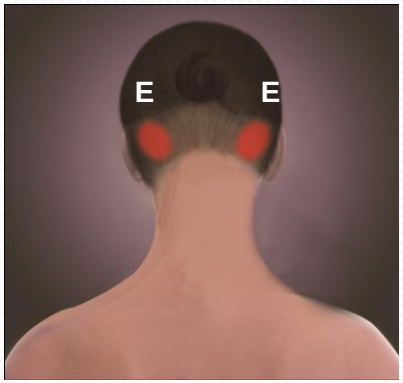
B. Procerus: no additional

C. Frontalis: no additional

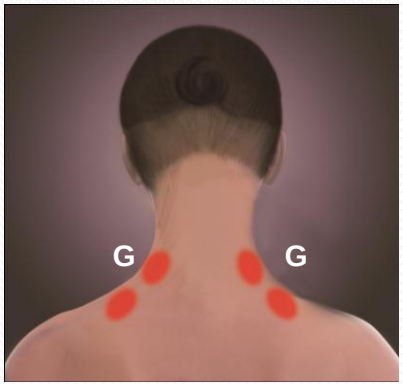


D. Temporalis: 5 U/site (up to 2 additional sites)

Sitting



E. Occipitalis: 5 U/site (up to 2 additional sites)



F. Cervical paraspinal: no additional

G. Trapezius: 5 U/site (up to 4 additional sites)

0.1 mL = 5 U/site

Blumenfeld A. *et al. Headache* 2010; 50:1406-1418

SUMMARY

- Chronic migraine is classified by the ICHD as ≥15 headache days/month for >3 months, of which ≥8 are migrainous
- 45,000 Kiwis, 13 per GP!
- Often suffer in silence
- SNOOP4
- Consider Onabotulinumtoxin A– the only medication specifically licensed by regulators for prophylaxis of headache in this population together with Migraine specific physiotherapy

Classification and diagnosis: conclusions[1]

- **Take-home message**: current practical, clinical definition is headache of more than 4 hours ≥15 days/month and prior or current diagnosis of migraine, with or without medication overuse
- There is a proven treatment for our 45,000 patients

1. Manack A *et al*. *Headache* 2009;**49**:1206–1213.

THANK YOU

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Sapphire Migraine Clinic Auckland
www.sapphireclinic.co.nz ph: 09 360 0066

Introduction to migraine

- Migraine distinguished from common headaches in the late 18th century[1]
- Further explored and diagnosed in the 19th century[1]
- Classification of migraine still evolving today
- Ranked by WHO as 19th among all causes of years lived with disability[2]
- Heavy burden of illness for the patient and a high cost for the economy[3,4]
- Treatment options evolving
  - Unmet need still exists for many patients

1. Silberstein SD *et al.* (Eds). *Atlas of Migraine and Other Headaches*. Second Ed. London and New York: Taylor and Francis Group, 2005.
2. World Health Organization. Headache disorders, 2004. http://www.who.int/mediacentre/factsheets/fs277/en. Accessed May 2010.
3. Lipton RB *et al*. *Neurology* 2007;**68**:343−349.
4. Andlin-Sobocki P *et al*. *Eur J Neurol* 2005;**12**(Suppl 1):1−27.

Migraine: the typical stages of an attack[1]

Premonitory phase
- Experienced by only 50% of patients
- Causes irritability, depression, tiredness, food cravings, unusual bursts of energy
- Can be hours or 1–2 days prior to attack

Aura
- Lasts 10–30 minutes
- Can affect vision on one side: blank patches, bright or flashing lights or coloured zigzag lines
- Possibly sensory symptoms: pins-and-needles, numbness (starting in fingers, progressing up the arms to the face)
- Difficulty speaking or finding the right words

Pain
- Can last for a few hours to 2–3 days
- Severe, one-sided headache, most commonly at the front or in the template but can occur on both sides of and anywhere in the head
- Throbbing or pounding headache which is made worse by movement
- Often accompanied by nausea. Vomiting may seem to relieve the headache
- Patient may want to avoid light and noisy situations, preferring to be alone in the dark

Resolution
- Final stage
- Headache fades but may leave the patient feeling tired, irritable, depressed, with difficulty concentrating
- Can take a further day before the patient has fully recovered

1. World Health Organization (WHO) in collaboration with the European Headache Federation (EHF). *J Headache Pain* 2007;**8**:S1–S47.

Botox Treatment for Chronic Migraine Patient Diary

How is migraine diagnosed and classified?

FLAG Description/example

• Systemic symptoms or sec. risk factors	Fever, weight loss or known cancer, HIV, immunosuppression, or thrombotic risks.
• Neurological symptoms or abn signs	Confusion, impaired alertness/ drowsy, or persistent focal signs (lasting more than 1 hour).
• Onset	'First and worst headache', sudden or abrupt from sleep, or progressively worsening.
• Older	New onset and progressive, e.g. after 50 years of age for giant cell arteritis.
• Previous headache history Triggered headache By Valsalva activity, exertion, or sexual intercourse	First headache or fundamentally different (i.e. significant change in features, frequency, or severity).

Cost

- Initial consultation charge when referred by their GP
- 30min consult $154
- First treatment subsidised by Allergan total cost $437
- Followup visit at two weeks and at 12 weeks $77
- Additional Botox every 12 weeks $1560
- Physiotherapy strongly recommended for all patients

Publications

- 2011 Journal of Cosmetic Dermatology, Vol 10, pages 93-96 "Phosphatidyl Choline Lipolysis and Hyaluronic Acid Augmentation to Enhance Non-Surgical Lower Facial Contouring Using Botulinum Toxin Type A, Drs Garsing Roger Wong and Wen-Pei Chen".

  2006 September The Journal of Sexual Medicine, Vol. 3 Issue 5 Page 892 Vardenafil Improved Erectile Function in a "Real-Life" Broad Population Study of Men with Moderate to Severe Erectile Dysfunction in Australia and New Zealand, Research Investigator for Bayer/GlaxoSmithKline Vardenafil Trial SB-782528-020.

Patents

- United States Patent Application 61/476,111 Method for Treating Eyelids filed 15 april 2011 Application No 61/476,111

- Referred to by Palomar as GET – Garsing Eye Treatment using 1540nm Fractional Erbium Glass Laser.

Migraine and Botulinum Toxin Type A

- Positive effects of Botox on migraine headache were shown in a study by (Brin et al 2002, Blumenfeld et al,2003 effective prophylactic treatment who conducted a multicenter open-label trial.
- Efficacy was categorised as either complete response with total symptom elimination,
- partial response with greater than 50% reduction in headache severity and frequency, or
- no beneficial response.
- Results showed that 51% of patients treated with Botox as a migraine prophylaxis reported a complete response to localised head and neck injections, with a mean duration of 4.1 months.
- An additional 38% reported partial improvement, with a mean response of 2.7 months.

Economic impact of migraine and chronic migraine

What have I observed?

- With respect to migraine headaches, the cortical spreading depression (the cause of aura) has been suggested to activate the trigeminal system *(Johnson et al)*
- The involvement of the ophthalmic division of the trigeminal nerve and its overlap of structures innervated by branches of C2 nerve roots
- This explains the typical distribution of migraine over the frontal and temporal regions, and the referral of pain to the parietal, occipital, and high cervicogenic regions.
- It is these factors that could explain the strong relationship between the inflammatory neurogenic and cervicogenic components which seem to be a cause of migraine headaches *(Schmitt et al, & Johnson et al)*
- And this cervicogenic component may explain the important role that manipulative therapy and postural muscle imbalance correction has in the treatment of cervicogenic headaches and migraine.