BOTOX: TO INJECT OR NOT INJECT? IN CHRONIC MIGRAINE PROPHYLAXIS

JENNIFER SHIN, PHARMD
PGY2 AMBULATORY CARE PHARMACY RESIDENT
COMMUNITYCARE HEALTH CENTERS
PHARMACOTHERAPY ROUNDS
OCTOBER 20, 2017

OBJECTIVES

- State the definition, background, and pathophysiology of chronic migraines (CM)
- Identify the current guideline recommendations for standard treatment
- Discuss outcomes from literature about botox and its place in therapy for CM prophylaxis

2

PATIENT CASE

- RW is a 35 year old female
- PMH: DM2, HTN, migraines, asthma, and seasonal allergies
- Current regimen:
  - Sumatriptan 25 mg twice daily PRN migraines
  - Topiramate 100 mg daily

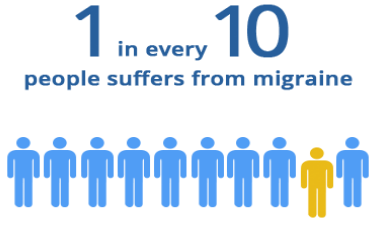
How many of you would say this is an appropriate regimen?

3

CHRONIC MIGRAINES

4

EPIDEMIOLOGY



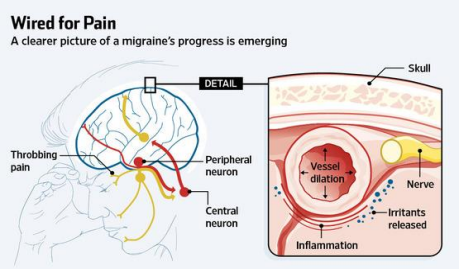
 5

EPIDEMIOLOGY

- Ranked 19th by the World Health Organization (WHO) among causes for years lived with disability
- Often begins at puberty and most affects those aged between 35 and 45 years
- More common in women, usually by a factor of about 2:1

Current Pain and Headache Reports, 16(1), 86–92. 6

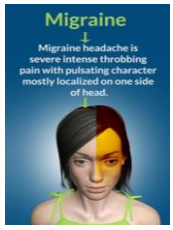
PATHOPHYSIOLOGY



The Neurology & Headache Treatment Center

BACKGROUND

- Divided into two groups based on headache days per month
- Can present with or without aura
- Headache attacks
- Clinical presentation
  - Throbbing headache
  - Nausea, vomiting, diarrhea
  - Lightheadedness
  - Dizziness



https://www.epainassist.com/headache/diagnosis-of-headach

DEFINITION

- Chronic migraines(CM) is:
  - A headache (HA) occurring on at least 15 days per month
  - For more than 3 months
  - With typical features of migraine on at least 8 days per month

American Headache Society

RISK FACTORS

- Modifiable
  - Obesity
  - Depression
  - Medication overuse
  - Sleep related problems
  - Caffeine overuse
- Non-modifiable
  - Age
  - Female sex
  - Caucasian race
  - Low educational level/socioeconomic status
  - Head injury

Curr Pain Headache Rep. 2012 Feb; 16(1): 86–92.

DIAGNOSIS: INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS

1. At least five attacks fulfilling criteria (2)–(4)
2. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
3. Headache has at least two of the following four characteristics:
   a) Unilateral location
   b) Pulsating quality
   c) Moderate or severe pain intensity
   d) Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

Headache Classification Committee of the International Headache Society (IHS)

DIAGNOSIS: INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS

4. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
5. Not better accounted for by another ICHD-3 diagnosis.

Headache Classification Committee of the International Headache Society (IHS)

GOALS OF THERAPY

- Reduce attack frequency, severity, and disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
- Improve quality of life
- Avoid acute headache medication escalation
- Educate and enable patients to manage their disease to enhance personal control of their migraine
- Reduce headache-related distress and psychological symptoms

Headache Classification Committee of the International Headache Society (IHS) 13

PROPHYLAXIS INITIATION

Initiate	• At least six headache days per month • At least four headache days with at least some impairment • At least three headache days with severe impairment or requiring bed rest
Consider	• Four to five migraine days per month with normal functioning • Two to three migraine days per month with some impairment • Two migraine days with severe impairment
Not indicated	• Less than four headache days per month and no impairment • Zero or one headache day per month regardless of impairment

Neuropsychiatric Disease and Treatment 2013:9 14

OPTIMIZING THERAPY

- Start at a low dose
- Give each preventive medication an adequate trial, > 2 months
- Reevaluating therapy and follow up is important
- Choose a drug based on efficacy, patient's preferences, headache profile, the drug's side effects, and the presence or absence of coexisting or comorbid conditions

15

AHS/AAN AND NICE GUIDELINE RECOMMENDATIONS: PROPHYLAXIS MANAGEMENT

- Initiate therapy with medications that have the highest level of evidence-based efficacy
- Initiate therapy with the lowest effective dose of the drug
- Avoid interfering medications (e.g., overuse of acute medications)
- Use of a long-acting formulation may improve compliance

Neurology April 24, 2012 vol. 78 no. 17 1337-1345 16

AMERICAN ACADEMY OF NEUROLOGY AND THE AMERICAN HEADACHE SOCIETY GUIDELINES FOR PROPHYLAXIS

	Level A	Level B
Antiepileptic drugs	Divalproex sodium	
	Topiramate	
β blockers	Propranolol	Atenolol
	Metoprolol	Nadalol
	Timolol	
Triptans (MRM*)	Frovatriptan	Naratriptan
		Zolmitriptan
Antidepressants		Amitriptyline
		Venlafaxine
NSAIDs		Ibuprofen/Naproxen
Herbals/vitamins/minerals	Petasites	Magnesium, Riboflavin, Histamines

*MRM = Menstrual related migraines

Neurology April 24, 2012 vol. 78 no. 17 1337-1345 17

PATIENT CASE

- Current regimen:
  - Sumatriptan 25 mg twice daily PRN migraines
  - Topiramate 100 mg daily
- Headache diary
  - 18 headache days per month
  - 5-6 months
  - Migraine features 10 days per month

How many of you would say this is an appropriate regimen?

A) True
B) False
C) Still not sure

18

BOTOX BACKGROUND

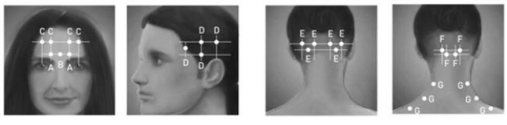
ONABOTULINUMTOXINA

BOTOX® (ONABOTULINUMTOXINA)

- A potent purified neurotoxin complex produced by anaerobic bacteria Clostridium botulinum
- Approved October 2010 for prophylaxis in adult patients with CM
- Dosing: 155 units once every 12 weeks
  - Equally divided and administered bilaterally, into 31 total sites

Lexicomp Online® , Pediatric & Neonatal Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; August 21 2017.

BOTOX® (ONABOTULINUMTOXINA)



A. Corrugator: 5 U each side

B. Procerus: 5U (one site)

C. Frontalis: 10 U each side

D. Temporalis: 20 U each side

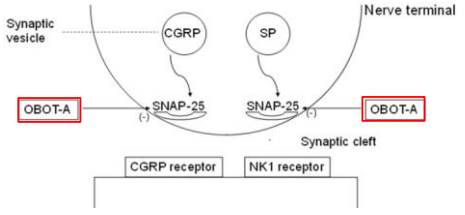
E. Occipitalis: 15 U each side

F. Cervical paraspinal: 10 U each side

G. Trapezius: 15 U each side

Lexicomp Online® , Pediatric & Neonatal Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; August 21 2017.

BOTOX SUSPECTED MECHANISM



Toxins (Basel). 2015 Jul; 7(7): 2659–2673.

BOTULINUM TOXIN IN THE MANAGEMENT OF CHRONIC MIGRAINE: CLINICAL EVIDENCE AND EXPERIENCE.

- PREEMPT I (n=679)
  - Primary endpoint: reduction of migraine episodes (non-significant)
  - Significant differences in reduction of headache and migraine days
- PREEMPT II (n=705)
  - Primary endpoint: confirmed efficacy of botox in reduction of headache days
- Identical study design, slightly different end points
- Commonly reported adverse events: neck pain, injection site pain, and eyelid ptosis
- Led to the approval of botox in prophylaxis of chronic migraine

Ther Adv Neurol Disord. 2017 Feb; 10(2): 127–135.

BOTOX: GUIDELINE RECOMMENDATIONS

- Guidelines of the American Academy of Neurology state that botox is effective and should be offered to patients with CM
- NICE guidelines recommend botox as a prophylaxis medication treatment for CM in patients who did not respond to at least 3 prior prophylaxis therapies

BOTOX FOR CHRONIC MIGRAINE: SAFE AND EFFECTIVE? WHEN SHOULD WE USE IT?

CLINICAL QUESTION

25

ONABOTULINUMTOXINA FOR CHRONIC MIGRAINE: EFFICACY, SAFETY, AND TOLERABILITY IN PATIENTS WHO RECEIVED ALL FIVE TREATMENT CYCLES IN THE PREEMPT CLINICAL PROGRAM

AURORA, ET AL (2014)

26

METHODS: AURORA, ET AL

- Objectives: Assess efficacy, safety and tolerability of botox as headache prophylaxis in adults with chronic migraine
- Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT)
- 24 week, double-blind, parallel-group, placebo controlled phase followed by a 32-week open-label phase
- Botox or placebo every 12 weeks for two cycles, followed by botox for three cycles

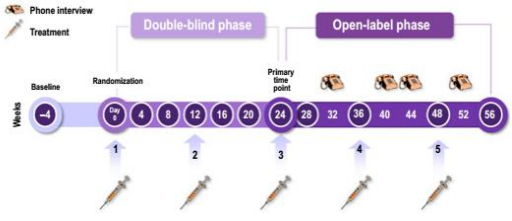
27

METHODS: AURORA, ET AL

- Inclusion
  - Patients that completed all five cycles
  - 18-65 years with a history of migraine defined by International classification of headache disorders
  - Had to have headache occurring on ≥15 days/4 weeks, with each day consisting of ≥4 h of continuous headache, and ≥50% of headache days being migraine or probable migraine days
  - Experience ≥4 distinct headache episodes, each lasting ≥4 h during this period
  - Naïve to botox prior to trial
- Exclusion
  - Headache prophylactic medication within 4 weeks prior to start date of baseline

28

METHODS: AURORA, ET AL



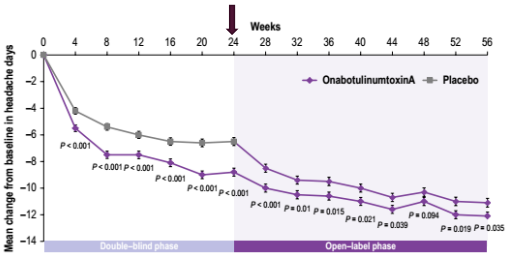
29

METHODS: AURORA, ET AL

- Primary endpoint
  - Frequency of headache days at 24 weeks
- Secondary endpoint
  - Frequency of migraine days
  - Moderate/severe headache days
  - Headache episodes
  - Migraine episodes
  - Acute headache medication intake

30

RESULTS: AURORA, ET AL



31

RESULTS: AURORA, ET AL

	24 weeks		
Mean change from baseline	Botox	Placebo	P value
Frequency of HA days	-8.8	-6.5	<0.001
Frequency of migraine days	-8.6	-6.2	<0.001
Frequency of moderate/severe HA days	-8.2	-5.8	<0.001
Total cumulative HA hours on HA days	-121.8	-82.0	<0.001
Frequency of HA episodes	-5.9	-4.8	<0.001
Frequency of migraine episodes	-5.5	-4.4	<0.001
Frequency of acute HA medication intakes	-10.4	-9.3	0.263

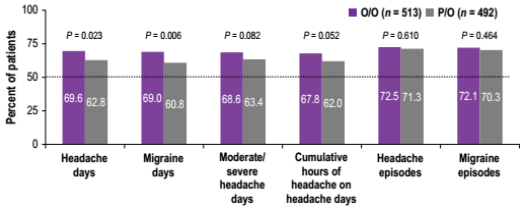
32

RESULTS: AURORA, ET AL

	56 weeks		
Mean change from baseline	Botox	Placebo	P value
Frequency of HA days	-12.0	-11.1	**0.035**
Frequency of migraine days	-11.6	-10.7	**0.038**
Frequency of moderate/severe HA days	-11.0	-10.1	**0.042**
Total cumulative HA hours on HA days	-166.8	-151.2	0.063
Frequency of HA episodes	-8.1	-7.5	0.057
Frequency of migraine episodes	-7.5	-7.0	0.088
Frequency of acute HA medication intakes	-16.1	-16.1	0.939

33

RESULTS: AURORA, ET AL



34

AUTHOR'S CONCLUSIONS

- Patients treated earlier with botox had better outcomes at week 56
- There is a continued need and cumulative benefit over time with continued prophylaxis
- Botox is a safe and effective option for use in CM

35

CRITICAL APPRAISAL

- Strengths
  - Well designed and largest trial thus far investigating use of botox in CM
  - Resulted in FDA approval for botox use in CM
  - Revealed earlier treatment with botox had better outcomes
- Weaknesses
  - Placebo response noted in both studies
  - Lacking report on differences between those with or without medication use headaches

36

UTILIZATION AND SAFETY OF ONABOTULINUMTOXINA FOR THE PROPHYLACTIC TREATMENT OF CHRONIC MIGRAINE

MATHARU, ET AL (2017)

37

METHODS: MATHARU, ET AL

- Objectives: Examine utilization patterns and safety of botox for prophylactic treatment of chronic migraine in routine clinical practice
- Prospective, observational post-authorization study
- Data collection
  - First study injection then every 3 months
    - ≤ 52 weeks for utilization
    - ≤ 64 weeks for safety data

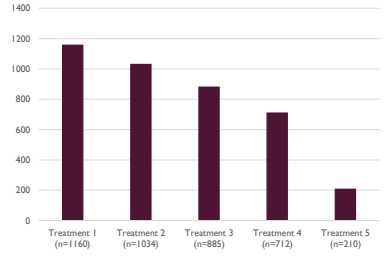
38

METHODS

- Inclusion
  - Botox treated and Botox naïve patients recruited by their physicians
  - 18 years or older with a new or established physician diagnosis of CM
  - Decision to initiate or continue treatment was independent of patient's enrollment in the study.
  - Completed at least one botox treatment session

39

RESULTS: MATHARU, ET AL



- 4017 botox treatment sessions administered total

40

RESULTS: MATHARU, ET AL

	n (%)
Patients with ≥ 1 adverse event	478 (41.2)
Serious adverse events	61 (5.3%)
Treatment discontinued due to adverse event	51 (4.4%)
Fatal adverse events	2 (0.2%)
Patients with ≥ 1 treatment related adverse event	291 (25.1%)
Serious treatment related adverse event	1 (< 0.1%)
Fatal treatment related adverse events	0 (0%)

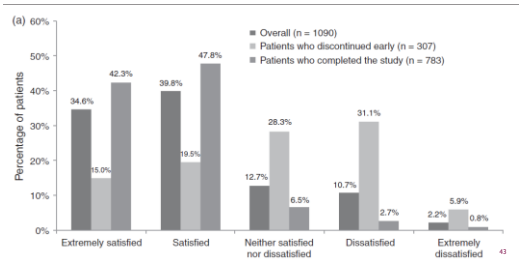
41

RESULTS: MATHARU, ET AL

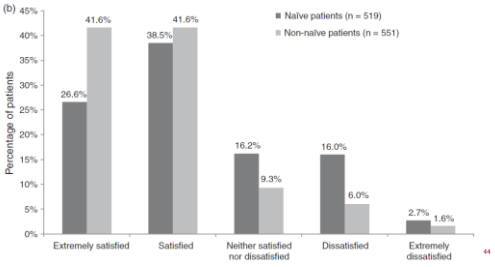
Adverse events,n (%)	Treatment naïve patients (n=556)	Overall (n=1160)
Neck pain	30 (5.4)	51 (4.4)
Eyelid ptosis	24 (4.3)	47 (4.1)
Muscular weakness	16 (2.9)	31(2.7)
Headache	14 (2.5)	26 (2.2)
Musculoskeletal stiffness	14 (2.5)	23 (2.0)
Migraine	12 (2.2)	34 (2.9)
Facial paresis	7 (1.3)	15 (1.3)
Facial spasm	7 (1.3)	11 (0.9)
Myalgia	7 (1.3)	11 (0.9)
Pruritus	7 (1.3)	7 (0.6)
Musculoskeletal pain	6 (1.1)	10 (0.9)

42

RESULTS: MATHARU, ET AL



RESULTS: MATHARU, ET AL



AUTHOR'S CONCLUSIONS

- Adverse event findings are similar to the PREEMPT studies
- Adverse event incidence rate decreased with each treatment session
- Data adds onto support the favorable safety profile of botox for CM prophylaxis

CRITICAL APPRAISAL

- Strengths
  - Observe and assess patient with CM in a real world setting
  - Large observational study in multiple settings
- Weaknesses
  - Observational study: increases generalizability

A MULTI-CENTER DOUBLE-BLIND PILOT COMPARISON OF ONABOTULINUMTOXINA AND TOPIRAMATE FOR THE PROPHYLACTIC TREATMENT OF CHRONIC MIGRAINE.

CADY, ET AL (2011)

METHODS: CADY, ET AL (2011)

- 3-center double-blind randomized pilot study
- Objectives: Direct comparison of topiramate vs onabotulinumtoxinA
  - Group 1 : Topiramate plus placebo injections
  - Group 2: onabotulinumtoxinA injections plus placebo tablets
- Daily headache diaries over 4 week baseline period and 12-week active study period

METHODS: CADY, ET AL (2011)

- Inclusion
  - 18 to 65 years of age
  - Subjects met criteria for CM as defined by Second Edition of the International Classification for Headache Disorders
- Exclusion
  - Female subjects who were pregnant, breast feeding, or planning to become pregnant
  - Individuals with headache disorders other than CM
  - Subjects who had previously used botulinum toxin of any type or topiramate regardless of indication

49

METHODS: CADY, ET AL (2011)

- Primary endpoint
  - Physician global assessment: treatment responder rate
  - Indicated improvement in both groups over 12 weeks
- Secondary endpoint
  - Measured at weeks 4 and 12
    - Headache days per month, migraine days, headache free-days, days on acute medication, and severity of headache episodes

50

RESULTS: CADY, ET AL (2011)

Week 4	Group 1 Topiramate	Group 2 Botox	P-value
	N=27	N=28	0.3221
No change	4 (14.8)	9 (32.1)	
Slight improvement	8 (29.6)	10 (35.7)	
Moderate improvement	9 (33.3)	3 (10.7)	
Marked improvement	3 (11.1)	4 (14.3)	

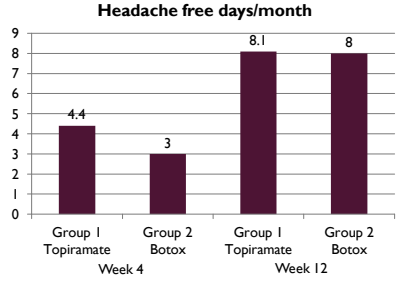
51

RESULTS: CADY, ET AL (2011)

Week 12	Group 1 Topiramate	Group 2 Botox	P-value
	N=24	N=24	0.9914
No change	5 (20.8)	3 (12.5)	
Slight improvement	1 (4.2)	5 (20.8)	
Moderate improvement	6 (25.0)	4 (16.7)	
Marked improvement	10 (41.7)	10 (41.7)	

52

RESULTS: CADY, ET AL (2011)



53

AUTHOR'S CONCLUSIONS

- Topiramate and botox demonstrated efficacy in treating subjects with CM
- Improvements were noted from both medications
- Support the use of botox for patients with frequent migraine

54

CRITICAL APPRAISAL

- Strengths
  - Completed a direct comparison between the two drugs
  - Subjects were asked to pursue an open label
- Weaknesses
  - Small sample size
  - Questionable blinding due to injection reactions
  - Lack a placebo arm

55

LITERATURE SUMMARY

Aurora, et al	Matharu, et al	Cady, et al
• Botox vs. placebo • Safety and efficacy • Reduced frequency of HA and migraine days with botox	• Botox observational • Safety and tolerability • Safety outcomes similar to PREEMPT trials	• Botox vs. topiramate • Efficacy • Similar efficacy outcomes

56

RW PATIENT CASE

- Assessment:
  - Controlled on current regimen
    - Topiramate 100mg daily
    - Sumatriptan 25mg twice daily PRN

Is this patient a candidate for Botox?

No: Patient is currently controlled on current regimen

57

CONCLUSION

- Diagnosis and treatment for chronic migraines is complex and clinicians should be mindful refractory to treatment is common.
- Botox has proven safety outcomes and efficacy outcomes in primary endpoints for reducing migraine days
- Guidelines of the American Academy of Neurology and NICE both recommend botox in CM
- Would recommend for patients that have failed two previous agents level A and/or B medications

58

FUTURE TOPICS FOR RESEARCH

- Studies comparing botox vs other approved agents on the market
- Studies to determine if botox reaches a plateau effect
- Studies in patients with comorbidities in addition to CM
- Studies to determine impact of botox on indirect and direct costs of CM compared to the agents well studied in CM

59

ACKNOWLEDGEMENTS

- Review committee
  - Jason Jokerst, Pharm.D., BCPS
  - April Hinds, PharmD, BCACP
- Evaluator
  - Lucas Hill, PharmD, BCPS

60

BOTOX: TO INJECT OR NOT INJECT? IN CHRONIC MIGRAINES

JENNIFER SHIN, PHARMD
PGY2 AMBULATORY CARE PHARMACY RESIDENT
COMMUNITYCARE HEALTH CENTERS
PHARMACOTHERAPY ROUNDS
OCTOBER 20, 2017