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

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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

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?

CHRONIC MIGRAINES

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
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

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

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

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)
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.
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

PROPHYLAXIS INITIATION

| Initiate | At least six headache days per month |
| Consider | At least four headache days with at least some impairment |
| Not indicated | Less than four headache days per month and no impairment |

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

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

PATIENT CASE

- Current regimen: Sumatriptan 25 mg twice daily PRN migraines,
  Topiramate 100 mg daily
- Headache diary
  10 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

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

<table>
<thead>
<tr>
<th>Antiepileptic drugs</th>
<th>Level A</th>
<th>Level B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β blockers</td>
<td>Propranolol</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Nadolol</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triptans (MRM*)</td>
<td>Frovatriptan</td>
<td>Naratriptan</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline</td>
<td>Venlafaxine</td>
</tr>
</tbody>
</table>

NSAIDs
- Ibuprofen/Naproxen

Herbals/vitamins/minerals
- Petasites
- Magnesium, Riboflavin, Hctamine

*MRM = Menstrual-related migraines
**BOTOX BACKGROUND**

**ONABOTULINUMTOXINA**

1. **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

2. **Guidelines of the American Academy of Neurology state that botox is effective and should be offered to patients with CM**

3. **NICE guidelines recommend botox as a prophylaxis medication treatment for CM in patients who did not respond to at least 3 prior prophylaxis therapies**

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**BOTOX SUSPECTED MECHANISM**

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

**CLINICAL QUESTION**

**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

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**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)

**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

**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
**RESULTS: AURORA, ET AL**

**56 weeks**

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

**24 weeks**

<table>
<thead>
<tr>
<th>Mean change from baseline</th>
<th>Botox</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of HA days</td>
<td>-8.8</td>
<td>-6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of migraine days</td>
<td>-8.6</td>
<td>-6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe HA days</td>
<td>-8.2</td>
<td>-5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cumulative HA hours on HA days</td>
<td>-121.8</td>
<td>-82.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of HA episodes</td>
<td>-5.9</td>
<td>-4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of migraine episodes</td>
<td>-5.5</td>
<td>-4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of acute HA medication intakes</td>
<td>-10.4</td>
<td>-9.3</td>
<td>0.263</td>
</tr>
</tbody>
</table>

**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

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

MATHARU, ET AL. (2017)

METHODS

- 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

RESULTS: MATHARU, ET AL

- Patients with ≥ 1 adverse event: 478 (41.2%)
- Serious adverse events: 61 (5.3%)
- Treatment discontinued due to adverse event: 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%)

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

CODY, ET AL (2011)

METHODS: CODY, 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

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

RESULTS: CADY, ET AL (2011)

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Group 1 Topiramate</th>
<th>Group 2 Botox</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>N=27</td>
<td>N=28</td>
<td>0.3221</td>
</tr>
<tr>
<td>Slight improvement</td>
<td>8 (29.6)</td>
<td>10 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>9 (33.3)</td>
<td>2 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Marked improvement</td>
<td>3 (11.1)</td>
<td>4 (14.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 12</th>
<th>Group 1 Topiramate</th>
<th>Group 2 Botox</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>N=24</td>
<td>N=24</td>
<td>0.9914</td>
</tr>
<tr>
<td>Slight improvement</td>
<td>1 (4.2)</td>
<td>5 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>6 (25.0)</td>
<td>4 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Marked improvement</td>
<td>10 (41.7)</td>
<td>10 (41.7)</td>
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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
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

LITERATURE SUMMARY

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aurora, et al</td>
<td>Botox vs. placebo</td>
<td>Safety and efficacy</td>
</tr>
<tr>
<td>Matharu, et al</td>
<td>Botox observational</td>
<td>Safety and tolerability</td>
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<tr>
<td></td>
<td></td>
<td>Safety outcomes similar to PREEMPT trials</td>
</tr>
<tr>
<td>Cady, et al</td>
<td>Botox vs. topiramate</td>
<td>Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Similar efficacy outcomes</td>
</tr>
</tbody>
</table>

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

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

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

ACKNOWLEDGEMENTS

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