Limb Pain (Tendonitis, Osteoarthritis, Plantar Fasciitis, Piriformis Syndrome)

Martin Taylor, DO, PhD
Neurology / OrthoNeuro
Clinical Associate Professor, Neurology
Ohio University College of Osteopathic Medicine
Columbus, OH
Disclosures

- Consultant/independent contractor: Allergan plc, and Ipsen Biopharmaceuticals, Inc.
- Speaker’s Bureau: Allergan plc, Avanir Pharmaceuticals, Inc. Depomed Inc., and Ipsen Biopharmaceuticals, Inc.
Questions

1. Which limb pain condition has the strongest literature supporting the use of botulinum toxin?
   a. Carpal tunnel syndrome
   b. Reflex sympathetic dystrophy
   c. Hip pain
   d. Lateral epicodylitis
   e. Shoulder pain
2. What is the most common dose range of onabotulinumtoxinA used in clinical trials for joint pain?

a. 5 to 10 units
b. 25 to 50 units
c. 50 to 100 units
d. 100 to 200 units
e. 300 to 500 units
3. True or False. The most common side effect reported in clinical trials after botulinum toxin injections for epicodylitis was grip weakness.

- True
- False
Botulinum Toxin Therapy for Joint and Limb Pain

- Shoulder Pain
- Hip Pain, Piriformis Syndrome
- Knee Pain
- Plantar Fasciitis
- Epicondylitis
Shoulder Pain
Long Term Effects of Intra-articular Botulinum Toxin A for Refractory Joint Pain

- Open label, prospective
- 9 subjects (osteoarthritis, RA, and psoriatic arthritis)
- Onabot (Botox) 50-100 units intra-articular
- Duration of effect 3 to 12 months
- No immediate or delayed adverse effects

Long Term Effects of Intra-articular Botulinum Toxin A for Refractory Joint Pain

Increased Active Range of Motion

- Flexion: 67% (p < 0.01)
- Abduction: 42%

Long Term Effects of Intra-articular Botulinum Toxin A for Refractory Joint Pain

Reduction in Shoulder Pain

Pretreatment: 8.2
Posttreatment: 2.4

(p <0.001)

Intra-articular Botulinum Toxin Type A: A New Approach to Treat Arthritis Joint Pain

- Double blind, placebo controlled
- 36 Subjects with shoulder pain refractory to NSAIDS, intra-articular steroid injection
- Onabot (Botox) 100 units + lidocaine vs saline + lidocaine (Intra-articular)
- Response measured at 4 weeks

Intra-articular Botulinum Toxin Type A: A New Approach to Treat Arthritis Joint Pain

Pain Reduction at 4 Weeks Post Treatment

Onabot: 61% (p < 0.002)
Saline: 31%

Intra-articular Botulinum Toxin Type A: A New Approach to Treat Arthritis Joint Pain

>30% reduction in pain

Intra-articular botulinum toxin A for Refractory Shoulder Pain: a Randomized, Double-blinded, Placebo-controlled Trial

- Double blind, placebo controlled
- 43 Subjects with moderate-severe arthritis shoulder pain
- Onabot (Botox) 100 units/lidocaine vs saline/lidocaine
- Reduction of pain at one month s/p injection
  - Reduction in pain on VAS: Onabot -2.4 vs saline -0.8 (p=0.014)
  - Improvement in SF-36 scores: Onabot (p</=0.035)
  - Clinically meaningful pain relief: Onabot 61% vs saline 36% (p=0.22)

Hip Pain
Piriformis Muscle

MUSCLE FUNCTION ON THE ASYMMETRIC PELVIS

ILIOLUMBAR LIGAMENTS
POSTERIOR INTEROSSEOUS LIGAMENTS
SACROTUBEROUS LIGAMENTS
Sacrospinous Ligament
HAMSTRING MUSCLES

THE PIRIFORMIS MUSCLE SUPPORTS THE FUNCTION OF THE SACROSPINOUS LIGAMENT
Inflamed Sciatic Nerve
Piriformis Injection
Efficacy of Botulinum Toxin Type A Treatment of Functional Impairment of Degenerative Hip Joint: Preliminary Results

- Open label, prospective
- 39 Subjects (41-82 y/o) with hip pain and osteoarthritis
- Abobot (Dysport) 400 units injected into the ipsilateral adductor longus/adductor magnus muscles

- Improvement in Harris Hip Score at 2, 4, and 12 wks (p<0.0001)
- Decrease in VAS pain scores at 2, 4, and 12 wks (p<0.001)
- Improved hip mobility noted on exam

## Botulinum toxin in Piriformis Syndrome

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study</th>
</tr>
</thead>
</table>
| Childers Martin K, et. al.* | Botulinum toxin type A use in piriformis muscle syndrome.  
| Fishman Loren M. et. al.* | Botox and physical therapy in the treatment of piriformis syndrome.  
| Lang Amy M.              | Botulinum Toxin Type B in Piriformis Syndrome.  
Study Design

- Single center, double blind, single group, crossover
- n=10
- Two 10 week treatment arms with 4 weeks washout
- BoNT-A (Botox) 100 U vs. preservative free normal saline
Botulinum Toxin Use in Piriformis Syndrome: A Pilot Study

Assessment

- VAS reporting of:
  - Pain Intensity
  - Spasm
  - Interference with Activities
  - Distress
- H-reflex measurement side-side / pre-post BoNT/A
- Pain-on-motion analysis (pain perceived during a stepping task)

Botulinum Toxin Use in Piriformis Syndrome: A Pilot Study

Results

– Functional improvement noted with BoNT/A injections (p<0.05)
– VAS decreases were detected under every category in BoNT/A treated group (p<0.05)
– Similarities in H reflex latencies between groups
  • Before injection of study treatments
  • Following injection of study treatments
– Motion analyses also failed to detect differences between baseline and experimental groups
– No adverse events were reported

Authors’ Conclusions

– “VAS data suggest that intramuscular piriformis injection with 100 units of botulinum toxin type A (Botox) can reduce pain to a greater extent than similar injections with vehicle alone.”

BoNT-A and Physical Therapy in the Treatment of Piriformis Syndrome

- **Study Design**
  - Double blind, placebo controlled, clinical trial
  - n=87, (n=67 after exclusion of those with <2 follow up visits)
  - BoNT/A (Allergan) 200 U, Lidocaine with steroid, or placebo
  - Standard physical therapy protocol twice weekly X 12 weeks
  - Examinations every 2 weeks
  - 1<sup>o</sup> endpoint: VAS Responses at two last visits (10 and 12 weeks)

- **Patient Selection**
  - Piriformis syndrome was diagnosed when there were significant discrepancies between anatomic position and FAIR position (per Snow BJ et. al. Neurology 1990;40(suppl 1):382)

**BoNT-A and Physical Therapy in the Treatment of Piriformis Syndrome**

### Results

<table>
<thead>
<tr>
<th>Injection</th>
<th>No. of Patients</th>
<th>No. Improved</th>
<th>% Improved **</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/L*</td>
<td>31</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>BoNT/A (Allergan)</td>
<td>21</td>
<td>13</td>
<td>65</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

*T/L* = triamcinolone and lidocaine

** Percent of subjects with 50% or more improvement at each of their last two visits


Authors’ Conclusion:

“Botox and Physical Therapy were more effective in treating Piriformis Syndrome than either T/L or placebo injections in conjunction with Physical Therapy.”

No Adverse events were reported in this study.
**BoNT-B in Piriformis Syndrome**

**Study Design**
- Single center, outpatient, open label study
- $n = 20$
- Follow ups at 2, 4, 8, 12, and 16 weeks
- 5000 units per piriformis (up to 10,000 units total dose if bilateral injection) infiltrated with EMG guidance

**Endpoints:**
- Mean VAS for buttock and hip pain and for low back pain.
- VAS for general and low back pain, pain radiating into lower limbs, and tingling.

BoNT-B in Piriformis Syndrome

Results

- Significant reductions in VAS
- Patient rated pain improvement:
  - 95% - fair to excellent
  - 75% - good to excellent
- Investigator rated efficacy:
  - 90% - fair to excellent
  - 55% - good to excellent

BoNT-B in Piriformis Syndrome

Safety

- Six patients (30%) experienced mild to severe dry mouth
- Two patients (10%) experienced mild to moderate flu like symptoms
- Two patients (10%) reported visual disturbance (10%)
- One patient (5%) reported dizziness
- One patient (5%) reported nausea
- One patient (5%) reported GERD

Intra-articular Botulinum Toxin Type A: a New Approach to Treat Arthritis Joint Pain

- Double blind, placebo controlled
- 42 Subjects with knee pain refractory to NSAIDS, intra-articular steroid injection
- Onabot (Botox) 100 units+lidocaine vs saline+lidocaine

Knee pain reduction on McGill Pain Joint Inventory Scale:
- Onabot superior to saline:
  - 1 month (p=0.011)
  - 3 months (p=0.002)

Intraarticular Botulinum Toxin A For Refractory Painful Total Knee Arthroplasty: A Randomized Controlled Trial

- Randomized, Placebo controlled, triple-blinded
- 49 subjects with painful total knee arthroplasty, mean duration 4.5 years
- Onabot (Botox) 100 units vs saline
- Single intra-articular injection into painful knee

Intraarticular Botulinum Toxin A For Refractory Painful Total Knee Arthroplasty: A Randomized Controlled Trial

- Reduction in VAS rated pain:
  - Onabot 71% vs saline 35%
  - s/p 2 months (p=0.28)  s/p 3 and 4 months (p=0.019)

- Duration of meaningful pain relief:
  - Onabot 39.6 days vs saline 15.7 days (p=0.045)

- Onabot superior to saline:
  - Western Ontario McMaster Osteoarthritis Index physical function (p=0.026)
    - Reduction in stiffness (p=0.004) and total score (p=0.024)
  - Reduction of pain subscale score on SF-36 (p=0.049)

An Open Label Pilot Investigation of the Efficacy Of Botulinum Toxin Type A [Dysport] Injection in the Rehabilitation of Chronic Anterior Knee Pain

- Open label Pilot Study
- 8 Subjects with >6 months of anterior knee pain, who had failed conservative therapy
- Obabot (Dysport) 300-500 units into distal 2/3 of VL followed by home exercise program to improve recruitment of the VM

- Subjects reported reduced knee pain and brace dependency
- Subjects reported increased participation in sporting and daily living activities

Treatment of Refractory Anterior Knee Pain Using Botulinum Toxin Type A (Dysport) Injection to the Distal Vastus Lateralis Muscle: A Randomized Placebo Controlled Crossover Trial

- Randomized placebo controlled crossover
- 24 subjects with refractory anterior knee pain
- Abobot (Dysport) 500 units vs saline injections to the vastus lateralis followed by home exercises focusing on re-training the vastus medialis

14 subjects received BoNT-A and 10 placebo injection.

Improvement at 12 weeks was significantly greater for Abobot compared with placebo-injected subjects for:

- AKPS (p<0.03)
- pain on kneeling (p<0.004),
- squatting (p<0.02)
- level walking (p<0.04).

Plantar Fasciitis
Plantar Fascia Injection
Treatment of Pain Attributed to Plantar Fasciitis with Botulinum Toxin A: A Short Term, Randomized, Placebo Controlled, Double-Blind Study

- Double blind, placebo controlled
- 27 Subjects (43 feet)
- Onabot (Botox) 70 units

Treatment of Pain Attributed to Plantar Fasciitis with Botulinum Toxin A: A Short Term, Randomized, Placebo Controlled, Double-Blind Study

Improvement in all measurements at 3 & 8 weeks

At 3 weeks:
- 39% decrease on the Pain Visual Analog Scale (p<0.005)
- 34% improvement of the Maryland Foot Score (p< 0.001)
- 40% increase in pressure algometry response (p<0.003)

Maintained at 8 weeks

No side effects reported

Ultrasonographic Guided Botulinum Toxin Type A Treatment for Plantar Fasciitis: An Outcome-Based Investigation for Treating Pain and Gait Changes

- Double blind, placebo controlled
- 50 subjects with unilateral plantar fasciitis
- Onabot (Botox) 50 units vs saline

Pain reduction on VAS in Onabot group superior to placebo at 3 wks and 3 months (p<0.001)
Center of pressure velocity during loading in Onabot group increased compared to placebo (p<0.05)
Fat pad thickness remained unchanged

Randomized Controlled Study of the Efficacy of the Injection of Botulinum Toxin Type A versus Corticosteroids in Chronic Plantar Fasciitis: Results at One and Six Months

- Single blind, placebo controlled
- 52 subjects
- Onabot (Botox) vs corticosteroids
- Outcomes based on Foot Health Square Questionnaire results at 1 and 6 months

one month (improvement with botulinum toxin vs. corticosteroid):
- pain 19.10/-6.84 (P = 0.001)
- function 16.00/-8.80 (P < 0.001)
- footwear 13.48/-7.95 (P = 0.004)
- self-perceived foot health 25.44/-5.41 (P < 0.001).
Treatment of Chronic Plantar Fasciitis with Botulinum Toxin A--An Open Pilot Study on 25 Patients with a 14-Week-Follow-Up

- Open label pilot study
- 25 subjects refractory to conservative therapy
- Dose finding: 6 subjects injected with Abobot (Dysport) 100 units and 6 subjects injected with Abobot (Dysport) 200 units.
- 13 subjects then injected with Abobot (Dysport) 200 units
- A significant reduction of maximum and continuous pain was seen 2 weeks after injection in the group of 19 patients treated with 200 units BoNT A and persisted until the end of the follow-up
- No adverse reactions reports

Tennis Elbow
Lateral Epicondyle Injection
Treatment of Lateral Epicondylitis with Botulinum Toxin: A Randomized, Double-blind, Placebo-controlled Trial

- Double blind, placebo controlled
- 60 subjects
- Onabot (Botox), 60 units vs. saline

- Decreased pain at weeks 4 & 12
- Mean decreased VAS 65 to 25 (p<0.006) at 4 wks
- No significant difference in grip strength
- 60% reported some weakness

Onabot 60 units vs. Placebo
Lateral Epicodylitis

Botulinum Toxin Injection in the Treatment of Tennis Elbow: A Double-blind, Randomized, Controlled, Pilot Study

- Double blind, placebo controlled
- 40 subjects (Failed steroid injection)
- Onabot (Botox) 50 units vs. saline
- IM injections were performed 5 cm distal to the maximum point of tenderness at the lateral epicondyle
- Trend toward improvement at 3 months
- No significant difference in grip strength
- 60% reported some weakness
- 12/18 reported extensor weakness

Treatment of Chronic Radial Epicondylitis with Botulinum Toxin A: A Double-blind, Placebo-controlled, Randomized Multicenter Study

- Double blind, placebo controlled
- 130 subjects
- Abobot (Dysport) 60 units vs. saline
- Decreased pain (VAS) at 2, 6, 12, and 18 weeks (=0.003)
- Subjective improvement at 6 and 18 weeks (<0.001)
- Improved grip strength in both groups
- Extensor weakness at 2 weeks

Use of Anatomic Measurement to Guide Injection of Botulinum Toxin for the Management of Chronic Lateral Epicondylitis: A Randomized, Controlled Trial

- Double blind, placebo controlled
- 60 subjects (refractory lateral epicondylitis)
- Onabot (Botox), 60 units vs. saline
- VAS (100 mm scale) at 4, 8, & 16 wks.

# Pain score at rest

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Group; mean (SD)</th>
<th>Difference in mean (95% CI)</th>
<th>p value (repeated measurement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>48.8 (23.7)</td>
<td>2.3 (−9.5 to 14.2)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Week 4</td>
<td>20.4 (15.9)</td>
<td>14.1 (5.8 to 22.3)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>17.9 (18.0)</td>
<td>11.5 (2.0 to 21.4)</td>
<td></td>
</tr>
<tr>
<td>Week 16</td>
<td>3.9 (6.0)</td>
<td>12.6 (7.7 to 17.8)</td>
<td></td>
</tr>
<tr>
<td>Outcome measure</td>
<td>Group; mean (SD)</td>
<td>Difference in mean (95% CI)</td>
<td>p value (repeated measurement)</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Baseline</td>
<td>65.8 (22.0)</td>
<td>65.0 (18.3)</td>
<td>0.8 (−10.9 to 12.6)</td>
</tr>
<tr>
<td>Week 4</td>
<td>52.0 (23.3)</td>
<td>57.4 (18.2)</td>
<td>5.3 (−6.8 to 17.5)</td>
</tr>
<tr>
<td>Week 8</td>
<td>43.8 (23.1)</td>
<td>51.5 (20.1)</td>
<td>7.8 (−4.8 to 20.4)</td>
</tr>
<tr>
<td>Week 16</td>
<td>18.8 (10.0)</td>
<td>30.6 (15.6)</td>
<td>11.8 (4.2 to 19.4)</td>
</tr>
</tbody>
</table>
## Pain score during maximum pinch

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Group; mean (SD)</th>
<th>Difference in mean (95% CI)</th>
<th>p value (repeated measurement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>42.6 (26.5)</td>
<td>45.1 (19.0)</td>
<td>2.4 (−11.0 to 15.9)</td>
</tr>
<tr>
<td>Week 4</td>
<td>17.2 (16.8)</td>
<td>32.7 (12.6)</td>
<td>15.4 (6.8 to 24.1)</td>
</tr>
<tr>
<td>Week 8</td>
<td>12.2 (14.9)</td>
<td>26.6 (11.3)</td>
<td>14.4 (6.8 to 22.2)</td>
</tr>
<tr>
<td>Week 16</td>
<td>5.1 (9.7)</td>
<td>13.6 (8.3)</td>
<td>8.5 (3.1 to 13.9)</td>
</tr>
</tbody>
</table>
## Reported Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse reaction; time frame</th>
<th>Group; no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Botulinum toxin</td>
</tr>
<tr>
<td><strong>Pain at injection site</strong></td>
<td></td>
</tr>
<tr>
<td>After injection</td>
<td>3</td>
</tr>
<tr>
<td>Weeks 0–4</td>
<td>7</td>
</tr>
<tr>
<td>Weeks 4–8</td>
<td>0</td>
</tr>
<tr>
<td>Weeks 8–16</td>
<td>0</td>
</tr>
<tr>
<td><strong>Tingling sensation around injection site</strong></td>
<td></td>
</tr>
<tr>
<td>After injection</td>
<td>0</td>
</tr>
<tr>
<td>Weeks 0–4</td>
<td>5</td>
</tr>
<tr>
<td>Weeks 4–8</td>
<td>0</td>
</tr>
<tr>
<td>Weeks 8–16</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subjective feeling of muscle spasm around injection site</strong></td>
<td></td>
</tr>
<tr>
<td>After injection</td>
<td>0</td>
</tr>
<tr>
<td>Weeks 0–4</td>
<td>8</td>
</tr>
<tr>
<td>Weeks 4–8</td>
<td>0</td>
</tr>
<tr>
<td>Weeks 8–16</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>23</td>
</tr>
</tbody>
</table>
Botulinum Toxin Therapy for Joint and Limb Pain

Summary

- **Good** data for BTX use in lateral epicondylitis and knee pain
- **Evolving** data for BTX in plantar fasciitis and shoulder pain
- **Minimal** data for BTX in hip pain, Except Piriformis Syndrome
Questions

1. Which limb pain condition has the strongest literature supporting the use of botulinum toxin?
   a. Carpal tunnel syndrome
   b. Reflex sympathetic dystrophy
   c. Hip pain
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   e. Shoulder pain
2. What is the most common dose range of onabotulinumtoxinA used in clinical trials for joint pain?

a. 5 to 10 units  
b. 25 to 50 units  
c. 50 to 100 units  
d. 100 to 200 units  
e. 300 to 500 units
3. True or False. The most common side effect reported in clinical trials after botulinum toxin injections for epicodylitis was grip weakness.

- True
- False
Thank You