Application of Botulinum Neurotoxin in the Treatment of Male & Female Sexual Dysfunction

Wayne J.G. Hellstrom, MD, FACS
Professor of Urology
Chief, Section of Andrology
Tulane University Medical Center
Disclosures

- Abbvie - Consultant or Advisor
- Allergan - Consultant or Advisor
- Boston Scientific - Consultant or Advisor
- Coloplast – Consultant or Advisor, Investigator
- Endo – Consultant or Advisor, Investigator, Lecturer
- Futura- Consultant or Advisor
- New England Research Institutes, Inc.- Investigator
- NIH – Board Member, Officer, Trustee
- Pfizer- Consultant or Advisor
- Theralogix – Board Member, Officer, Trustee
The Origins of the Botulinum Neurotoxin

- First reports of Botulism syndrome attributed the condition to proteins in bad sausages.

- Misconceptions regarding the cause of Botulism were cleared up in 1897 when Dr. Emile Pierre Marie Van Ermengen, a German Professor of Microbiology, isolated and grew Clostridium Botulinum and described its toxin.

- Seven different serotypes of Botulinum Neurotoxin (BoNT) have been identified (BoNT-A, B, C, D, E, F, and G).

Emile Pierre Marie Van Ermengem 1851–1922

Erbguth et al. *Journal Neural Transm* 2008
The Structure of BoNT

- Proteolytic cleavage of precursor polypeptide chain leads to formation of heavy and light chains and toxin activation

- All serotypes composed of heavy chain (100 kD) and light chain (50 kD) interconnected by a disulfide bond

- Heavy chain or B (Binding) component, recognizes and attaches to glycoprotein components on presynaptic cholinergic nerve terminals (i.e. NM jct)

- Light chain or A (Active) component, which is a metalloenzyme (zinc) endopeptidase, cleaves target proteins

Montecucco et al. *Molecular Microbiol* 1994
Normal Neurotransmitter Physiology

Rystedt et al. 2012
BoNT Mechanism of Action

Rystedt et al. 2012
**BoNT Strains and Formulations**

- Each BoNT strain targets different components of the SNARE complex and cleaves the target protein.
- Serotype-A (BoNT-A) is the most highly studied and commercially utilized for therapeutic purposes.
- While many commercial formulations of BoNT exist, within the United States, onabotulinumtoxinA (Botox®, Allergan, Inc., Irvine, CA), is the only brand that is licensed for use due to robust randomized controlled trial (RTC) data supporting its efficacy and safety.

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Cleavage Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>BoNT-A</td>
<td>SNAP-25</td>
</tr>
<tr>
<td>BoNT-B</td>
<td>VAMP</td>
</tr>
<tr>
<td>BoNT-C</td>
<td>SNAP-25, Syntaxin</td>
</tr>
<tr>
<td>BoNT-D</td>
<td>VAMP</td>
</tr>
<tr>
<td>BoNT-E</td>
<td>SNAP-25</td>
</tr>
<tr>
<td>BoNT-F</td>
<td>VAMP</td>
</tr>
<tr>
<td>BoNT-G</td>
<td>VAMP</td>
</tr>
</tbody>
</table>

Montecucco et al. *Molecular Microbiol* 1994
Dr. Alan Scott paved the way for the first FDA-approved use of BoNT for the treatment of strabismus, blepharospasm, and hemifacial spasm in 1989.

Current FDA approved uses of BoNT for urologic dysfunction:
- "Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication"
- "Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication"

With respect to sexual health, the use of BoNT for any of the purposes listed in this presentation are not currently FDA approved and as such are considered “off-label”
Male Sexual Dysfunction

1. Chronic Scrotal Pain
2. Premature Ejaculation
3. Penile Retraction
4. Erectile Dysfunction
5. Peyronie’s Disease

\[
\int e^x = f(u)^n
\]
1. Chronic Scrotal Pain

- Chronic Scrotal Pain (CSP) is all pain emanating from the testicles, epididymis, and scrotum.

- The estimated prevalence of CSP in males age 18 and older is between 0.4% and 4.75% and up to 50% of all cases are idiopathic in nature.
Chronic Scrotal Pain

Other potential etiologies include:

- Prior pelvic surgery (vasectomy, hernia/hydrocele repair, varicocelectomy)
- Trauma
- Infection (epididymitis, prostatitis)
- Medications
- Tumors
Current Therapeutic Options for CSP

First-line treatment options for CSP typically includes antibiotics, anti-inflammatories, and analgesics.

For cases of CSP refractory to these therapies, second-line oral agents such as antidepressants or anticonvulsants can be attempted.

If medical management alone fails to relieve CSP, patients can be offered regional nerve blocks, or more invasive treatments such as surgical denervation of the spermatic cord, orchiectomy, or epididymectomy.

Starke et al. Trans Androl Urol 2017
BoNT for CSP

- BoNT is a longer-acting alternative to nerve blocks
- One hundred units of Botox® are reconstituted in 10cc of saline and injected around the spermatic cord near the external inguinal ring
- The analgesic effects of Botox® in CSP are a result of the decreased release of substance P and calcitonin gene-related peptide (CGRP) leading to an inhibition of neurogenic inflammation and pain

Calixte et al. Curr Urol Rep 2017
Tojuola et al. performed Botox® injections in 25 men and found that at a median follow-up of eight months, 14% of patients had complete resolution of pain and 56% of patients had a >50% reduction in pain.

Calixte et al. performed Botox® injections in 44 CSP patients & at a median follow-up of 6 months, 7.5% of patients had complete resolution of pain & 55% of patients had a >50% reduction in pain.
2. Premature Ejaculation

ISSM Definition of Premature Ejaculation (PE):

- “characterized by ejaculation that always or nearly always occurs before or within one minute of vaginal penetration (intravaginal ejaculatory latency time [IELT]) and accompanying negative personal consequences such as distress, frustration, or the avoidance of sexual intimacy”

Determining prevalence of PE is difficult due to its negative social stigma, but it is estimated to affect around 12% of the male population.
Current Therapeutic Options for PE

- Off-label pharmacotherapy is the current basis of treatment for PE.

- SSRIs and topical anesthetics have consistently been shown to be efficacious, but long-term outcomes still need to be evaluated.

Serefoglu et al. Med Hypothesis 2010
Effects of BoNT on Male Rat Ejaculatory Behavior

- Proposed mechanism of action:
  - Rhythmic contraction of the bulbospongiosus muscles plays a role in ejaculation so injection of BoNT into these muscles blocks neural transmission and assists in delaying of ejaculation process

- Long-Evans rats (33 males)
- ~2 weeks to adapt to the light–dark cycle

1) Placebo: Saline injection (0.1 ml)  
2) Low Dose: Botulinum toxin-A (0.5 U in 0.1 ml)  
3) High Dose: Botulinum toxin-A (1 U in 0.1 ml)
Bulbospongiosus Muscle

Bulbospongiosus Muscle BoNT Injection

Serefoglu et al. *J Sex Med* 2014
The Effects of BoNT Injection on Male Rat Ejaculatory Behavior

* Paired-sample T-test

Serefoglu et al. *J Sex Med* 2014
Serefoglu et al. tested this hypothesis and injected the bulbospongiosus muscle of rats with saline, 0.5U Botox®, or 1U Botox®. The groups receiving 0.5U or 1U Botox® had a statistically significant increase in IELT compared to their pretreatment IELT.

Ongün et al. administered saline, 1U Botox®, or 5U Botox® percutaneously into the bulbospongiosus muscle of rats. The ejaculation latency time of the group receiving 5U Botox was statistically significantly longer vs the control group & the group receiving 1U of Botox (P = .003).
In a study by Li et al., a total of 69 men suffering from PE were given Botox® or placebo injections into the bulbospongiosus.

- Treatment group: 34 PE patients receiving injected dosage of 100U Botox®
- Control group: 35 PE patients receiving saline injections

At four weeks, the treatment group showed statistically significant increase in mean IELT (2.35 min +/- 1.83 min) compared to the control group (0.79 min +/- 0.21 min) and baseline (0.74 min +/- 0.27 min).

Li et al. Zhonghua Nan Ke Xue 2018
3. Penile Retraction and Flaccid Length

- Penile retraction occurs when smooth muscle fibers intertwined in Dartos fascia contract, which conceals part of the flaccid penis by pulling it inwards
  - Retraction triggered by cold, exercise, or stress

- May cause embarrassment in some men due to visibly decreased flaccid penile length that may be observed by their partner or other individuals in public changing areas such as locker rooms
Penile Retraction and Flaccid Length

- Penile retraction may not be a commonly described phenomena, but dissatisfaction with flaccid penile length is a prevalent issue

- As many as 27% of US men reported that flaccid penile length was a dissatisfying aspect of their genital image

Gaither et al. 2017
Current Therapies for Penile Retraction and Flaccid Length

Due to a lack of therapeutic options, men seeking to improve flaccid genital length are turning to more invasive options such as the Penuma implants and suprapubic lipectomies.

The outcomes of both techniques are currently still being investigated.

Elist et al. 2018
BoNT for Penile Retraction & Flaccid Length

- Shaeer et al. treated 10 men with bothersome penile retraction via intra-Dartos injection of 100 units of BoNT
  - After one round of injections, 70% of men reported a subjective improvement in amplitude and frequency of retraction, as well as improved flaccid length
  - Objective measurements showed slight improvements in flaccid penile length (mean of 2.5mm)
  - Improvements lasted up to six months in this trial, and there were no adverse events reported

In recent years, the aesthetics of male genitalia has become an area of interest for potential intervention.

Patients have demonstrated concerns regarding:
- scrotal size
- scrotal skin wrinkling
- excess scrotal perspiration

In an effort to improve these issues, some providers have proposed & treated patients with BoNT-A. This therapy has been termed *Scrotox*.
Scrotal Aesthetics

The outcomes, as explained by these providers, include:

- An enlarged appearance of scrotum due to relaxation of the cremasteric muscle
- Decreased scrotal wrinkles given relaxation of Dartos muscle
- Relief of CSP in those with concurrent complaints of pain
- The increased scrotal surface area is also theorized to promote heat loss and reduce perspiration

At present, no peer-reviewed literature on the safety & efficacy of these treatments exists on Pubmed and before any recommendations can be considered, more critical data regarding this therapy is necessary.
4. Erectile Dysfunction

Erectile dysfunction (ED) is defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance.

More than 30 million men in the United States and 150 million men worldwide are estimated to be affected by ED.

Potential etiologies include:
- Cardiovascular (arterial insufficiency)
- Endocrine (hypogonadism, diabetes mellitus)
- Neural dysfunction
- Peyronie’s disease
- Priapism
- Medication-induced
- Iatrogenic

Burnett et al. J Urol 2018
Erectile Dysfunction

- In the flaccid penis, cavernosal smooth muscle tissue is in a contracted state due to underlying sympathetic tone.
- Sexual stimulation triggers nitric oxide (NO) production from parasympathetic cholinergic and non-adrenergic non-cholinergic neurons.
- NO release causes cavernosal smooth muscle relaxation and a resultant increase in penile blood flow and tumescence.
- Penile tumescence compresses cavernosal veins against the thick tunica albuginea layer of the penis, which restricts the venous outflow of blood.
- The imbalance between inflow and outflow of blood causes an erection.
First-line Treatment
Phosphodiesterase type 5 inhibitors

Second-line Treatment
Intracavernosal injections | Vacuum erection devices | Transurethral therapies

Third-line Treatment
Penile Prosthesis
BoNT for ED

- BoNT treats ED via increased cavernosal smooth muscle relaxation
- Intracavernosal injection (ICI) of BoNT inhibits release of norepinephrine from sympathetic neurons, causing decreased α-adrenergic activation and increased relaxation of smooth muscle
- BoNT also blocks acetylcholine release from parasympathetic cholinergic neurons, which prevents generation of subendothelial nitric oxide, a vasodilator
- This means that cavernosal smooth muscle dilation becomes solely dependent on the release of neuronal nitric oxide from non-adrenergic non-cholinergic neurons

Ghanem et al. Sex Med Rev 2018
Ghanem et al. performed a clinical trial on 24 men with severe vasculogenic ED refractory to PDE5 inhibitors as diagnosed by penile duplex ultrasonography.

- Treatment group: ICI of Botox® (50U)
- Control group: 1mL ICI of 0.9% normal saline

The treatment group saw an increase in:

- Mean peak systolic velocity from 24.6 cm/s to 34.9 cm/s (p=0.005)
- Increase in the mean Sexual Health Inventory for Men (SHIM) score from 5.58 to 10.25 (p=0.0075)
- Increase in the mean Erection Hardness Score from 2 to 2.75 (p=0.01)

Seven members of the treatment group could engage in penetrative sex after administration of 100mg sildenafil compared to only two members of the control group.

Due to these positive results, Phase II randomized controlled trial of 160 patients has begun.
5. Peyronie’s Disease

- Peyronie’s Disease (PD): an acquired penile abnormality characterized by fibrosis of the tunica albuginea, which may be accompanied by pain, deformity, ED, and/or distress

- Prevalence rate ranges from 0.5% to 20.3% within specific populations

Peyronie’s Disease

- Etiology: acquired inflammatory disorder of tunica albuginea wherein trauma to penile shaft during erect or semi-erect state leads to cascade of:
  - Extravascular protein deposition
  - Decreased elastin content
  - Tunical collagen change from Type 1 to Type 3
- Collectively, these changes lead to tunical scarring or plaque formation
- Types of PD:
  - Active - patient has changing symptoms due to recent nature of inciting factor, curvature and plaque have not fully developed
  - Stable – symptoms have been unchanged for three or more months and curvature and plaque are fully developed

AUA Guideline. *J Urol* 2015
Current Therapies for PD

- Treatment options are largely based on patient symptomatology
  - If condition does NOT interfere with intercourse, can treat with conservative management (oral pain medications)
  - If condition interferes with intercourse, consider more invasive options
    - Intralesional Clostridium Histolyticum (CCH) injections
    - Surgical therapies: Tunical plication, plaque excision, or Inflatable penile prosthesis placement
BoNT for PD

- Only current data on BoNT for PD is a 2015 prospective cohort study
  - Sample: 22 patients aged >18 with stable PD
  - Possible mechanism of action: BoNT has been previously shown to reduce fibrosis in cell cultures and animal models of hypertrophic scars/keloids

- Study Outcomes:

<table>
<thead>
<tr>
<th></th>
<th>Degree of Curvature</th>
<th>Thickness of Plaque (cm)</th>
<th>Erectile Function (IIEF-5)</th>
<th>Pain (Visual Analog Scale Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Treatment</td>
<td>32.95 ± 9.21°</td>
<td>0.34 ± 0.20</td>
<td>16.18 ± 4.46</td>
<td>3.36 ± 3.48</td>
</tr>
<tr>
<td>Post-Treatment</td>
<td>25 ± 9.38°</td>
<td>0.27 ± 0.13</td>
<td>18.22 ± 4.55</td>
<td>1.14 ± 1.58</td>
</tr>
<tr>
<td>P-value</td>
<td>(P = .025)</td>
<td>(P = .014)</td>
<td>(P = .002)</td>
<td>(P = .001)</td>
</tr>
</tbody>
</table>

Muñoz-Rangel et al. *Urol* 2015
Female Sexual Dysfunction

1. Vestibulodynia
2. Dyspareunia
3. Vaginismus
4. Persistent Genital Arousal Disorder (PGAD)
Distinguishing Dysfunctions

1. Vestibulodynia = Pain with vestibule stimulation

2. Dyspareunia = Pain with penetrative intercourse

3. Vaginismus = muscle contraction prevents penetration
1. Vestibulodynia

- Pain in the vaginal vestibule following any kind of stimulation
- Affects 15% of women and exact etiology unknown
- Proposed risk factors include: inflammation, infection, neurologic, muscular, and genetic etiologies
- Current treatment options include: Cognitive behavioral therapy, topical anesthetics, antidepressants, and vestibulectomy
BoNT for Vestibulodynia

BoNT-A injection is gaining traction as a new therapeutic option

Mechanism of action: Injection of BoNT into bulbospongiosus muscle blocks release of calcitonin gene-related peptide (CGRP) and substance P

<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Mean follow-up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoon et al.</td>
<td>4</td>
<td>11 months</td>
<td>7 point reduction in VAS</td>
</tr>
<tr>
<td>Pelletier et al.</td>
<td>20</td>
<td>6 months</td>
<td>5 point reduction in VAS</td>
</tr>
<tr>
<td>Peterson et al.</td>
<td>64</td>
<td>6 months</td>
<td>7 point reduction in VAS</td>
</tr>
</tbody>
</table>

VAS: Visual Analog Scale, a measurement tool used to measure characteristic or attitude, such as pain, which cannot be easily quantified

Peterson et al. compared BoNT injections to saline controls using VAS

- Both groups had significant reductions in pain
- No significant difference between either group

Possible explanation: act of injecting has a therapeutic effect similar to acupuncture and causes a reduction in pain experienced by the patient
2. Dyspareunia

- Persistent or recurrent genital pain associated with sexual intercourse
- Affects 8-21% of women & can be classified into the following subtypes:
  - Superficial: involves the vulvar region or vaginal opening
  - Deep: involves the cervix or pelvic/uterine/abdominal region
  - Superficial and deep
- Associated with other female reproductive pathologies:
  - e.g. Conditions that present with superficial dyspareunia include:
    - Vulvovaginal infections, obstetric complications, muscular abnormalities, and more

Latthe et al. Sex Med Rev 2006
BoNT for Dyspareunia

BoNT may be a potential therapeutic option for dyspareunia secondary to myofascial pain syndrome

- a musculoskeletal condition in which myofascial trigger points are sensitized due to dysfunction in muscle and its surrounding connective tissue
- Myofascial trigger points are small, palpable nodules that are present within taut bands of muscle and produce sustained contraction when irritated
- If trigger points form within the pelvic region, a patient may experience dyspareunia

Current therapies for this condition include:
- First-line: Physical therapy or muscle relaxants
- Second-line: Injections of local anesthetics or steroids

Aredo et al. 2017
BoNT for Dyspareunia

- Mechanism of action: BoNT injections into levator ani region prevent excessive contraction or spasticity without inducing paralysis
- Additional mechanism of action: Local analgesic effect (unknown mechanism)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Mean follow-up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelowo et al.</td>
<td>29</td>
<td>2.5 weeks</td>
<td>79% reduced pain</td>
</tr>
<tr>
<td>Jarvis et al.</td>
<td>12</td>
<td>12 weeks</td>
<td>Reduced group VAS score</td>
</tr>
<tr>
<td>Morrissey et al.</td>
<td>21</td>
<td>6 months</td>
<td>83% reduced pain</td>
</tr>
<tr>
<td>Abbott et al.*</td>
<td>60</td>
<td>6 months</td>
<td>Reduced group VAS score</td>
</tr>
</tbody>
</table>

- *Abbott et al. used saline controls. Both the BoNT and control group showed significant reductions in VAS score

3. Vaginismus

- Disorder in which patient **cannot tolerate penetration** despite desire to do so
  - **Primary Vaginismus:** condition in which patient has never experienced non-painful intercourse
  - **Secondary Vaginismus:** condition in which a patient experienced non-painful intercourse prior to onset of symptoms
- Affects 5-17% of women
- Exact etiology unknown, but possible psychological component
- Muscle activity in vaginismus patients who are lightly touched or examined has been shown to be significantly increased on electromyograph (EMG) in the levator ani, puborectalis, and bulbocavernosus muscles, when compared to healthy controls

Reissing et al. *Female Sex Pain Disorder* 2009
Current therapeutic options for Vaginismus

- First-line therapies include: Physical therapy, Kegel exercises, sex and relationship counseling, psychotherapy and support groups
  - Oral medications commonly prescribed: Muscle relaxants and Anxiolytics
- Most common treatment plan involves utilization of vaginal dilators, with other treatments facilitating or supplementing dilator use

Pacik et al. 2011
BoNT for Vaginismus

Due to contracted musculature leading to vaginismus, BoNT injections into pelvic floor musculature has the potential to aid in treatment of refractory vaginismus by alleviating muscle tension

Shafik et al. used 5 saline controls. None of the controls could tolerate sexual intercourse

<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shafik et al.</td>
<td>8</td>
<td>100% tolerate sex</td>
</tr>
<tr>
<td>Ghazizadeh et al.</td>
<td>24</td>
<td>75% tolerate sex</td>
</tr>
<tr>
<td>Bertolasi et al.</td>
<td>39</td>
<td>63% tolerate sex</td>
</tr>
<tr>
<td>Pacik et al.</td>
<td>241</td>
<td>71% tolerate sex</td>
</tr>
</tbody>
</table>

Saline vs BoNT

- Many studies on BoNT include a control group who received injections of saline

- Vestibuloydnia and Dyspareunia
  - BoNT & saline injections both resulted in reduced symptoms

- Vaginismus
  - BoNT reduces symptoms but saline injections had no effect

- Saline injections may have a therapeutic effect for pain syndromes but not for syndromes related to muscle contraction

4. Persistent Genital Arousal Disorder

- Defined by a collection of five characteristics:
  1. Physiologic symptoms of sexual arousal
  2. Not resolving with orgasm
  3. Unrelated to subjective sexual desire or excitement
  4. Not necessarily triggered by sexual activity
  5. Symptoms are distressing and often painful

- Incidence and exact etiology of Persistent Genital Arousal Disorder (PGAD) unknown

Current Therapeutics for Persistent Genital Arousal Disorder

- No current standard of care therapeutic options
- SSRIs, SNRIs, dopamine agonists, antiepileptics, transcranial magnetic stimulation, surgery and more, have all been attempted with varying degrees of success
- Data limited largely to case reports
BoNT for Persistent Genital Arousal Disorder

- In 2014, a patient case-series was published on the use of periclitorial injections of BoNT-A for PGAD.
- Authors described two women suffering from PGAD with no discernable origin despite thorough medical and psychiatric workup.
- Results: No reporting of any objective scale to measure the degree to which PGAD was improved, but after six months, the women reported some amelioration of their symptoms.
- Hypothesized mechanism of action: inhibition of peripheral glutamate release, decreased CGRP release, and other molecules that are responsible for pain signaling.

Nazik et al. *J Sex Marital Ther* 2014
Conclusions

- BoNT is a potential therapeutic intervention for many male and female sexual pathologies.
- The risks, benefits, and outcomes of BoNT are still being actively investigated and more long-term data will be crucial to future implementation.
- At present, much of the data originates from animal models and single-center prospective studies indicating the need for more randomized controlled trials.
Thank You!