Application of Botulinum Neurotoxin in Male Sexual Dysfunction: Where Are We Now?

Amit G. Reddy, BS, Brian P. Dick, BS, Caleb Natale, BA, Kole P. Akula, BS, Ayad Yousif, MD, and Wayne J. G. Hellstrom, MD

ABSTRACT

Introduction: Botulinum neurotoxin (BoNT) is a recognized therapeutic agent of modern medical care, routinely used to treat medical conditions affecting a variety of organ systems including the musculoskeletal, integumentary, and urological domains. Ongoing research is exploring BoNT's potential role as a therapeutic agent for a variety of male sexual pathologies.

Objective: To review and analyze the literature regarding BoNT as a treatment option for male sexual dysfunction.

Methods: A PubMed search was performed for English-language articles in peer-reviewed journals between 1970 and 2019 (with one article from 1897). Relevant articles referenced within these texts were also included. One article did not have an accompanied English full-text available. The following search terms were used: "Botox", "Botulinum toxin", "Botulinum toxin A", "Onabotulinum A", "Abobutlinum A", "BoNT", "BoNT-A", "Male sexual health", "Male sexual pathology", "Peyronie's disease", "Premature ejaculation", "Scrotal Pain", "Penile Retraction", "Scrotox", "Erectile Dysfunction", and "Botox in Urology".

Results: There is interest in the potential role of BoNT in the treatment of male sexual pathologies. We identified studies that used BoNT to treat chronic scrotal content pain, premature ejaculation, erectile dysfunction, Peyronie's disease, penile retraction, and more. However, despite preclinical/clinical data indicating some potential efficacy and safety in these settings, a lack of robust clinical trial data has resulted in no current Food and Drug Administration–approved indications for the use of BoNT in the treatment of male sexual pathology. As a result, much of the current use of BoNT by today's providers is "off-label," and ongoing clinical trials aim to further elucidate the potential role of this therapeutic agent.

Conclusion: Current data suggest that BoNT could have a potential role as a treatment option for certain types of male sexual pathologies. However, more randomized controlled trial data regarding its long-term safety and efficacy are necessary before a widespread clinical adoption can take place. **Reddy AG, Dick BP, Natale C, et al. Application of Botulinum Neurotoxin in Male Sexual Dysfunction: Where Are We Now?. J Sex Med 2021;9:320–330.**

Key Words: Botulinum Neurotoxin; Botox; Male Sexual Dysfunction; Treatment; Research

INTRODUCTION

Botulinum neurotoxin (BoNT) is a commonly used therapeutic agent of modern medical care. It is routinely used to treat medical conditions affecting a variety of organ systems including, but not limited to, the musculoskeletal, integumentary, and urological systems. Although once believed to be a component within bad sausages that caused a deadly food-borne illness, the misconceptions were elucidated in 1897 when Dr Emile Pierre Marie Van Ermengen discovered the bacterium responsible for producing BoNT and the toxin's mechanism of action.[1,2] Further advances were made in 1981 when Dr Alan Scott published his data on the first successful clinical utilization of BoNT for the treatment of 42 individuals with strabismus.[3] Successful outcomes in this patient population paved the way for the first Food and Drug Administration (FDA)-approved use of BoNT for the treatment of strabismus and other ocular conditions in 1989.[4] Since these discoveries, the use of BoNT has expanded to many other areas of medicine, and successful treatment of a variety of pathologies has been reported. Within

Received October 31, 2019. Accepted May 21, 2020.

Department of Urology, Tulane University School of Medicine, New Orleans, USA

https://doi.org/10.1016/j.sxmr.2020.05.004

the field of men's health specifically, the use of BoNT has continued to increase, and ongoing research into its potential role as a therapeutic agent for a variety of sexual pathologies is being explored. This article is an up-to-date review of the current preclinical and clinical literature on the uses of BoNT for the treatment of male sexual dysfunction.

Understanding BoNT

BoNT, produced by bacterial strains within the *Clostridia* family, exists as 7 distinct serotypes (A B, C, D, E, F, and G).[5] Of these antigenically distinct serotypes, serotype-A (BoNT-A) is the most potent and commercially used for therapeutic purposes.[6,7] However, evidence for utilization of other serotypes including serotype-B has also expanded in recent years.[8,9] Currently, BoNT-A is globally available in 3 commercial formulations (onabotulinumtoxin A [Botox; Allergan, Inc, Irvine, CA], abobotulinumtoxin A [Dysport; Ipsen Biopharmaceuticals, Paris, France], incobotulinumtoxin A [Xeomin; Merz Pharmaceuticals GmbH, Frankfurt, Germany]), with each brand having its own pharmaceutical form, recommended dosage, and potency.[10,11] Within the United States, Botox is the only brand that is licensed by the FDA because of the robust randomized controlled trial data supporting its efficacy and safety in the treatment of a variety of medical pathologies.[12] For the remainder of this article, any mention of BoNT-A will refer to the Botox formulation specifically. If a study of interest has specifically used another serotype or formulation, the authors will make note of this. Finally, when commenting about BoNT without regard to any particular strain or formulation, the abbreviation BoNT will be used.

Structurally, all variants of BoNT are composed of a heavy chain (100 kD) and light chain (50 kD), which are interconnected by disulfide bonds.[13] These di-chain proteins adhere to a typical A-B structure, with each component of the toxin serving a specific role.[14] The heavy chain, or B (Binding) component, recognizes and attaches to glycoprotein components on presynaptic cholinergic nerve terminals. It is this glycoprotein-binding sequence that gives BoNT its high selectivity for peripheral cholinergic synapses.[15] After this binding process, the cell uses endocytosis to absorb the BoNT. Intracellularly, the disulfide bond is reduced, and the light chain, or A (Active) component, which is a metalloenzyme (zinc) endopeptidase, functions to cleave target proteins. Specifically, the BoNT disrupts the process of neurotransmitter exocytosis through targeting of the soluble *N*-ethylmaleimide sensitive factor attachment protein receptor (SNARE) complex.[16] This complex is composed of 3 specific proteins: synaptobrevin or vesicle-associated membrane protein, synaptosome-associated protein 25 kD (SNAP-25), and syntaxin-1[17] (Figure 1). Vesicle-associated membrane protein is located on the synaptic vesicle membrane, while SNAP-25 and syntaxin-1 are both located on the plasma membrane of the presynaptic nerve terminal. Of note, each BoNT strain targets different components of the SNARE complex, with BoNT-A cleaving the SNAP-25 component exclusively. The disruption of the SNARE complex leads to the inability of presynaptic vesicles to bind to the inner surface of the plasma membrane, thus preventing exocytosis and neurotransmitter release.

In humans, when the BoNT targets the cholinergic synapse of the neuromuscular junction, it blocks the release of

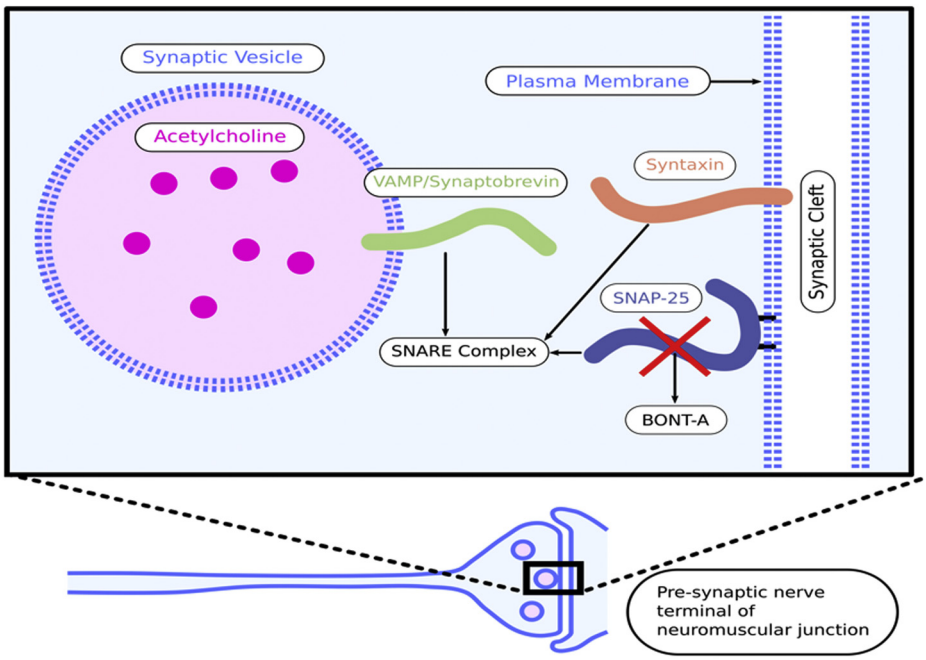

Figure 1. Botulinum neurotoxin mechanism of action at the presynaptic terminal. BONT-A = botulinum neurotoxin serotype-A; SNAP-25 = synaptosome-associated protein 25 kD; SNARE = soluble *N*-ethylmaleimide sensitive factor attachment protein receptor; VAMP = vesicle-associated membrane protein. Figure 1 is available in color online at www.jsm.jsexmed.org.

acetylcholine from presynaptic neurons, and as a result, there is a lack of postsynaptic acetylcholine receptor stimulation and subsequent temporary muscle weakness. The temporal and reversible nature of BoNT is theorized to be due to a combination of factors including the restoration of the SNARE protein complex, the creation of new nerve terminals and synaptic connections, and the recovery of the original nerve terminals over time.[15,18,19] A typical timeline of BoNT effects is outlined in Table 1.

FDA Approval and Safety Profile

As previously stated, BoNT-A is the only serotype that is widely used in the United States. The only current FDA-approved uses of BoNT-A for urological pathology are for the treatment of "urinary incontinence due to detrusor overactivity associated with a neurologic condition" and "overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have inadequate response to or are intolerant of an anticholinergic medication."[20] Accordingly, the use of BoNT-A for all other urological indications, including men's sexual health, is considered "off-label." As a result, it is extremely important for both patients and providers to understand the risks, benefits, and current literature regarding the use of BoNT-A in the treatment of male sexual pathology.

With respect to safety, BoNT has a range of potential adverse effects that vary in incidence and severity. In addition, the pharmacologic and safety profiles of BoNT can vary based on serotype and formulation. For the purpose of this discussion, the safety information will pertain only to BoNT-A. Despite BoNT-A being used as a localized, targeted therapy, patients and providers should be aware that individuals may have rare systemic adverse effects (Table 2). The mechanism behind these adverse effects is likely inadvertent toxin entry into the systemic circulation, which can reportedly cause generalized muscle weakness and even flu-like symptoms in some.[21,22] It is postulated that the risk of systemic effects is related to total injection dosage and injection frequency rather than weight-based dosage.[21] The dosages used in cases of certain urologic pathology, such as neurogenic bladder, have also been documented to potentially lead to these adverse effects.[23] While these symptoms can sometimes prompt the need for immediate medical attention, they follow the same course of any BoNT administration and are temporary, often lasting a period of few months before spontaneous resolution occurs. One population of patients that must be monitored with extra precaution for risk of systemic adverse effects are those with preexisting neuromuscular disorders such as myasthenia gravis or amyotrophic lateral sclerosis. While some providers argue that the use of BoNT-A is contraindicated in these patients, the FDA currently allows for use of therapeutic BoNT-A in this cohort but recommends close monitoring, given their increased risk of clinically significant adverse effects.[18,24] The less serious adverse effects of BoNT-A include but are not limited to focal muscle weakness, injection site reactions and pain, and other effects that are based on the location of BoNT administration.[25]

Table 1. Timeline of botulinum neurotoxin (BoNT) effects on muscle (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4658210/)

Approximate time following initial BoNT administration	Effect on target muscle
Several days	Initial muscle weakening
Several weeks	Peak muscle weakening
2 Months	Muscle weakening begins to subside
3 Months	Return to baseline muscle strength

Table 2. Possible side effects of botulinum neurotoxin (BoNT)

Potential systemic adverse effects of BoNT
Generalized muscle weakness
Asthenia
Ptosis
Dysphagia
Dysarthria
Urinary incontinence
Respiratory difficulties
Flu-like symptoms

While it is difficult to stratify the incidence rate and severity of adverse effects of BoNT-A, a 2004 systematic review and meta-analysis assessing the safety of BoNT-A specifically compiled 36 double-blinded, randomized studies treating a range of pathologies. The study found no serious adverse events and reported a 24.7% incidence rate of mild to moderate adverse events in the BoNT-A groups compared with a 15% rate in the control groups.[25] Unfortunately, the definitions of serious and mild to moderate adverse events varied according to the original investigators of each individual trial, and thus, it is difficult to fully extrapolate these data. However, within the literature, systemic adverse events are most often treated as serious adverse events, so it would not be an unreasonable assumption that this meta-analysis demonstrates very low rates of such serious events. In addition, the authors note that individual provider experience and optimized injection techniques can impact the rate of adverse events and must be taken into consideration when assessing BoNT-A safety.

There are currently minimal data on specific adverse effects occurring as a result of BoNT-A treatment of the sexual pathologies outlined in this review. This does not imply a lack of potential for such effects but rather illustrates the need for larger data sets and more robust randomized clinical trials.

METHODS

A PubMed search was performed for English-language articles in peer-reviewed journals between 1970 and 2019 (with one article from 1897). In addition, any relevant articles referenced within these texts were also included. Only one article did not

have an accompanied English full-text available. The following search terms were used: "Botox", "Botulinum toxin", "Botulinum toxin A", "Onabotulinum A", "Abobutlinum A", "BoNT", "BoNT-A", "Male sexual health", "Male sexual pathology", "Peyronie's disease", "Premature ejaculation", "Scrotal Pain", "Penile Retraction", "Scrotox", "Erectile Dysfunction", and "Botox in Urology".

RESULTS

Chronic Scrotal Content Pain

Chronic orchialgia is defined as unilateral or bilateral testicular pain that lasts at least 3 months. It can be intermittent or constant, but it must significantly interfere with day-to-day life to be clinically diagnosed.[26] Nickel et al define chronic epididymitis similarly, but expanded it to include pain affecting the scrotum, testicles, or epididymis.[27] Evidently, testicular pain is difficult to differentiate clinically from epididymal pain, as they share many sensory neurons,[28] and as a result, these 2 terms are often used interchangeably throughout the literature. For the purposes of this review, we will be using the term chronic scrotal content pain (CSP) to include any pain emanating from the testicles, epididymis, or scrotum.

The estimated prevalence of CSP in males aged 18 years and older is between 0.4% and 4.75%.[29,30] There is an increased prevalence after vasectomy alone in up to 33% of cases and after inguinal hernia repair alone in up to 62.9% of cases.[31] There are many known potential etiologies of CSP, including prior pelvic surgery (vasectomy, hernia repair, hydrocelectomy, varicocelectomy), direct trauma, infection (epididymitis, prostatitis, brucellosis), medications (amiodarone, imipramine withdrawal), vasculitides (polyarteritis nodosa, Behcet's syndrome), neuralgias, and even testicular malignancies.[32,33] However, the most common etiology is idiopathic pain, which is implicated in as many as 50% of cases.[26] The first-line treatment options for CSP can vary based on suspected etiology but typically include antibiotics, anti-inflammatory agents, and analgesics. For cases of CSP refractory to these therapies, second-line oral agents such as antidepressants or anticonvulsants can be attempted.[34] 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.[35]

While regional nerve blocks are an effective option for pain reduction, they are a short-acting therapy. BoNT-A is a potentially longer acting alternative to simple nerve blocks. The analgesic effects of BoNT-A in CSP are postulated to be a result of decreased release of substance P and calcitonin gene-related peptide, leading to inhibition of neurogenic inflammation and pain.[31] One hundred units of BoNT-A are reconstituted in 10 cc of saline and injected around the spermatic cord near the external inguinal ring. Tojuola et al performed BoNT-A injections in 25 men with CSP and found that at a median follow-up of 8 months, 14% of patients had complete resolution of pain and 56% of patients had >50% reduction in pain.[36] Similar results were found by Calixte et al who performed BoNT-A injections in 44 CSP patients.[31] At a median follow-up of 6 months, 7.5% of patients had complete resolution of pain, and 55% of patients had >50% reduction in pain. Both cohorts used a visual analog scale (VAS) to quantify changes in patient-reported pain, and neither group reported side effects or complications from BoNT-A administration. Finally, Khambati et al performed BoNT-A injections in 18 patients with CSP who had failed medical management but experienced pain relief with a prior spermatic cord-block.[35] After injections of 100 units of BoNT-A, patients at a median follow-up of 6 months reported a 22% reduction in pain measured using the VAS.[35] There were no reported side effects or complications. Notably, of the 18 patients who were initially treated, only 8 could be analyzed at 6 months, as the remaining patients had undergone additional procedures such as repeat BoNT-A injections or surgical intervention. Across all 3 studies, the duration of pain relief from a single administration of BoNT-A was in the order of months, which is significantly longer than the hours of pain relief provided by a standard spermatic cord-block. While RCTs are needed to validate these results, BoNT-A appears to be a potential treatment option for patients with CSP given its longer duration of action and minimal risk profile.

Premature Ejaculation

The International Society for Sexual Medicine defines premature ejaculation (PE) as a male sexual dysfunction characterized by ejaculation that always or nearly always occurs before or within 1 minute of vaginal penetration (intravaginal ejaculatory latency time [IELT]) and is accompanied by negative personal consequences such as distress, frustration, or the avoidance of sexual intimacy.[37] Determining the exact prevalence of PE is difficult because of its negative social stigma, but it is estimated to affect around 12% of the male population.[38] The etiology of PE is not completely understood, and while there may be some psychiatric components, the main pathology is believed to be a neurobiological process.[39,40] Thus, off-label pharmacotherapy is the current basis of treatment for PE. Medications such as selective serotonin reuptake inhibitors and topical anesthetics have consistently been shown to be efficacious, but long-term outcomes still need to be evaluated.[41]

On a neurological level, the process of ejaculation is a well-described spinal cord reflex involving the bulbospongiosus muscles. Specifically, rhythmic contraction of the bulbospongiosus muscles plays a role in ejaculation, and injecting BoNT-A into these muscles could block neural transmission and aid in delaying the ejaculation process.[41] Serefoglu et al tested this hypothesis and injected the bulbospongiosus muscle of rats with saline vehicle, 0.5 units of BoNT-A, or 1 unit of BoNT-A.[42] The groups receiving 0.5 units or 1 unit of BoNT-A had a statistically significant increase in IELT compared with their

pretreatment IELT, with peak effects noted 11 days after administration. The group that received saline vehicle had no significant differences when compared with pretreatment IELT and posttreatment IELT from both BoNT-A treatment groups. In a more recent preclinical study, Ongün et al used a para-chloroamphetamine model of ejaculation and studied how BoNT-A injections into the bulbospongiosus muscle could quantitatively affect ejaculation emission and expulsion.[43] 3 groups of 7 rats each were stratified into a control group, a group that received 1 unit of BoNT-A, and a group that received 5 units of BoNT-A. The toxin was administered percutaneously into the bulbospongiosus muscle, and measurements were taken 5 days after intervention. When comparing ejaculation latency times among the 3 groups, the rats receiving 5 units of BoNT-A had statistically significantly longer ejaculation latency times (1,092 ± 657 seconds) than the control group (298 ± 81 seconds) and the group receiving 1 unit of BoNT-A (439 ± 100 seconds). Notably, unlike the study by Serefoglu et al which found statistically significant increases in ejaculation latency times with both the 0.5 units and 1 unit of BoNT-A, this article only saw statistically significant increases with 5 units of BoNT-A.[42] This study also demonstrated that BoNT-A mediated its effects specifically on the expulsion phase of ejaculation. Parameters such as basal seminal vesicle pressure and seminal vesicle contraction rate, which served as markers of the emission phase of ejaculation, had no statistically significant changes. No adverse effects were reported in any of the animals in this study. However, it should be noted that one hypothesized side effect of administration of this therapy in humans is anejaculation, as contraction of the bulbospongiosus muscles play a role in propelling semen through the urethra during orgasm. Some limitations to this preclinical data include a lack of injection given to the control group, small sample sizes, and no long-term data on safety and length of effect. Also, in this study, an experimental model of ejaculation was used in rats with no baseline PE. Future studies accounting for these limitations and using experimental PE models may yield more reliable results.

There are also clinical studies attempting to understand the role of BoNT-A. In a human study of 69 patients by Li et al, a treatment group of 34 PE patients received an injection of 100 units of BoNT-A into the bulbospongiosus muscles and a control group of 35 PE patients received saline injections into the bulbospongiosus muscles.[44] At 4 weeks, the treatment group demonstrated a statistically significant increase in mean IELT (2.35 ± 1.83 min) compared with the control group (0.79 ± 0.21 min) and baseline (0.74 ± 0.27 min). A total of 6 patients had side effects from the therapy, which included 4 cases of decreased erectile hardness and 2 cases of incomplete urination. These changes resolved spontaneously without additional intervention and did not impair sexual function. Abdel-Meguid et al also used BoNT-A injections to treat PE but performed transurethral, intraprostatic injections.[45] In this trial, 24 men were given 100 units of BoNT-A injections and subsequently demonstrated a statistically significant increase in mean IELT at 6 months. However, these patients reported no significant improvement in "personal distress or interpersonal difficulty related to ejaculation" suggesting that improvements in objective measures of PE may not necessarily correlate to improved patient satisfaction and that there may be an underlying psychiatric component.[45] The mechanism through which intraprostatic BoNT-A injections affect IELT remains unknown at this time. One hypothesis revolves around the finding that a subset of patients who suffer from inflammatory conditions such as chronic prostatitis (specifically NIH category 2 or 3) have higher rates of PE than the general population for reasons not yet known.[46,47] Thus, injections of intraprostatic BoNT-A, which has been hypothesized to decrease the release of certain inflammatory mediators, could decrease intraprostatic inflammation and potentially provide beneficial effects for PE. There are currently multiple studies attempting to use BoNT-A to treat chronic prostatitis/chronic pelvic pain syndrome, in addition to other inflammatory conditions such as chronic migraines.[48–50] However, it should be noted that there are preclinical data suggesting that BoNT-A may not actually have any anti-inflammatory effects.[51] Another proposed hypothesis unrelated to the inflammatory pathway is that BoNT-A may be inducing chemical denervation of both the prostatic and ejaculatory ducts, which suppresses their contraction during emission and can thus delay ejaculation.[45]

There are minimal RCT data evaluating BoNT-A as a treatment for PE, and long-term safety data are sparse. Despite this, patents for the use of BoNT injection in the treatment of PE exist.[52] Gaxiola et al outlined 2 treatment protocols using 25 units and 50 units of BoNT-A injections.[52] The first method involves injections directly into the penile tissue, while the second method describes injections into the frenulum, prepuce, and glans penis. With respect to the initial method, given the high vascularity of the penis, some researchers argue that any penile BoNT-A administration is likely to diffuse into the systemic circulation and place the patient at risk for systemic side effects.[42] Animal and human studies using intracavernosal injections (ICIs) of BoNT-A in the treatment of erectile dysfunction (ED) have demonstrated that such risks are minimal and are mentioned later in this review. Overall, the current data on BoNT-A as a treatment option for PE provide a mixed picture with respect to efficacy and safety. In addition, many facets of this therapy such as cost and duration of action must also be considered before any implementation into clinical care.

Erectile Dysfunction

To understand how BoNT can treat ED, one must first review normal erectile physiology. In the flaccid penis, cavernosal smooth muscle tissue is in a contracted state because of underlying sympathetic tone. Sexual stimulation triggers nitric oxide production from parasympathetic cholinergic neurons and nonadrenergic noncholinergic neurons. Nitric oxide causes cav-

ernosal smooth muscle relaxation and a resultant increase in penile blood flow and tumescence. Penile tumescence compresses cavernosal veins against the thick overlying tunica albuginea layer of the penis, which restricts the venous outflow of blood. The imbalance between inflow and outflow of blood causes an erection.[53,54] ED is defined as the inability to achieve or maintain an erection that is sufficient for satisfactory sexual intercourse.[55] The global prevalence of ED is reported to range from 3% to as high as 76.5% in certain populations, with higher rates associated with increasing age.[56] The etiology of ED is often multifactorial and can be due to pathologies affecting any part of the erectile process, including cardiovascular (arterial insufficiency, subclinical endothelial dysfunction), endocrine (hypogonadism, hypothyroidism/hyperthyroidism, diabetes), or neural dysfunction (multiple sclerosis, epilepsy, spinal surgery).[38] The current stepwise treatment plan for the treatment of ED is outlined in Figure 2.

One hypothesis for the mechanism of action through which BoNT-A may treat ED stems from the treatment of priapism. In a patient with priapism, α-adrenergic agonists are injected directly into the corpora cavernosa to induce smooth muscle contraction and cessation of the erection process.[57] Contrarily, ICI of BoNT-A inhibits release of norepinephrine from sympathetic neurons, causing decreased α-adrenergic activation which may lead to increased relaxation of smooth muscle and facilitation of erection.[58] However, BoNT-A also blocks acetylcholine release from parasympathetic cholinergic neurons, which decreases generation of subendothelial nitric oxide. The end result is that cavernosal smooth muscle dilation becomes solely dependent on the release of neuronal nitric oxide from nonadrenergic noncholinergic neurons.[58] One issue with this theory is that BoNT-A has been shown to improve erectile function in men not responding to tri-mix.[58] Phentolamine, one of the drugs in tri-mix, is an α-adrenergic blocker which has the same proposed mechanism as mentioned previously. As BoNT-A is able to treat patients that tri-mix cannot, there are likely other unknown mechanisms through which it may mediate its effects. Ghanem et al performed ICIs of saline, 1 unit of BoNT-A, and 2 units of BoNT-A in rats (n = 30) and harvested penile tissue at 4 weeks after treatment. Compared with the control group, the penile tissue from the treatment groups had a statistically significant increase in mean resting sinusoidal diameter.[58] A larger mean resting sinusoidal diameter was also found by De Young et al in a separate rat study (n = 10); however, these findings did not reach statistical significance.[59]

There is currently only one completed human study on the use of BoNT-A for ED. Ghanem et al performed a clinical trial on 24 men with severe vasculogenic ED refractory to phosphodiesterase type 5 inhibitors and ICI with tri-mix, as diagnosed by penile duplex ultrasonography.[58] The treatment group received an ICI of 50 units of BoNT-A, and the control group received a 1-mL ICI of 0.9% normal saline. To reduce any risk of systemic toxicity, a compressing rubber band was placed at the base of the penis before ICI. The treatment group demonstrated an increase in mean peak systolic velocity from 24.6 cm/s to 34.9 cm/s ($P = .005$), an increase in the mean Sexual Health Inventory for Men score from 5.58 to 10.25 ($P = .0075$), and an increase in the mean Erection Hardness Score from 2 to 2.75 ($P = .01$). In addition, 7 members of the treatment group were able to engage in penetrative sex after administration of 100 mg of sildenafil compared with only 2 members of the control group. There were no side effects or complications related to systemic toxicity, indicating that ICI of BoNT-A can be used in a safe manner with minimal risk of systemic toxicity. Ghanem et al have begun a phase II RCT of 160 patients; the intervention group will receive an ICI of 100 units of BoNT-A and the control group an ICI of 1 mL of saline. Given the myriad of effective treatment options for ED, the threshold for widespread adoption of BoNT-A as a potential therapeutic agent remains high. However, if more RCTs can demonstrate its efficacy and safety over a longer duration than current therapies and in patients whose ED is refractory to treatments such as phosphodiesterase type 5 inhibitors, a potential niche may be possible in the future.

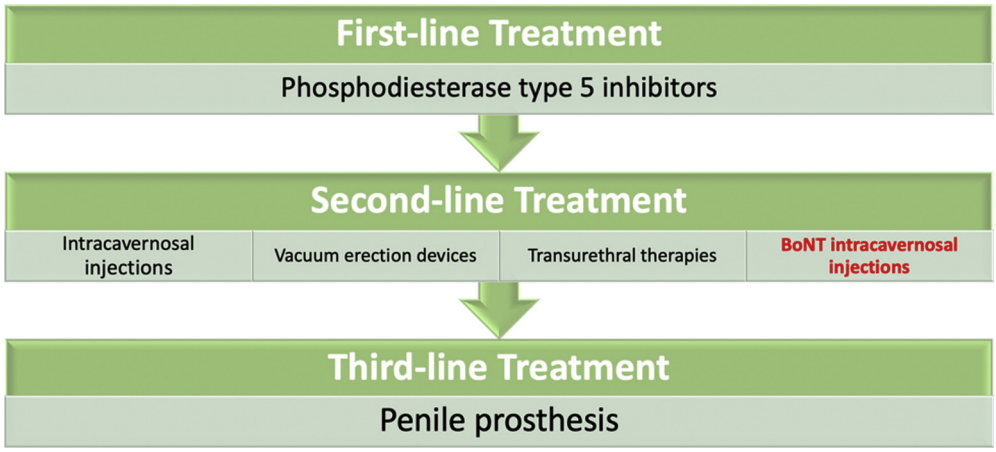

Figure 2. Erectile dysfunction stepwise treatment plan. BoNT = botulinum neurotoxin. Figure 2 is available in color online at www.jsm.jsexmed.org.

Peyronie's Disease

Peyronie's disease (PD) is an acquired penile disorder characterized by irregularities in local connective tissue that lead to changes in collagen composition and ultimately trigger the formation of an abnormal penile plaque or scar in the tunica albuginea layer.[60] While the exact etiology of PD is believed to be multifactorial in nature and still not thoroughly elucidated, current literature suggests that some form of penile trauma, such as during sexual intercourse, is key to triggering the abnormal healing cascade of PD.[61–63] The prevalence of PD is reported to range from 0.5% to as high as 20.3% in some specific patient populations.[64] The large variability in prevalence rates is likely due to differences in study methodology, definitions of PD, and the patient populations surveyed.

When considering therapeutic options for PD, it is important to accurately characterize the stage of the condition, as this along with other considerations (degree of curvature, effect on sexual intercourse, and overall quality of life) dictates the treatment options that should be offered to the patient. For patients with active phase PD, current first-line treatment options include nonsteroidal anti-inflammatory drugs, which treat penile pain but have no effect on plaque size or curvature.[64] While a host of other oral therapies are described in the literature for the treatment of active phase PD, their effectiveness is still being investigated, and at this time, they are not recommended by the American Urological Association.[64] Other interventions such as intralesional injections, extracorporeal shockwave therapy, and traction therapy have also been demonstrated to treat active phase PD; however, widespread adoption of these practices is limited, and they remain primarily as treatment options for stable PD.

In the stable phase of PD, the predominant symptom is penile curvature that interferes with sexual intercourse. The treatment of stable-phase PD includes many of the options previously mentioned but also includes surgical intervention, ranging from tunical plication or plaque incision/excision with grafting to placement of a penile prosthesis in men with concomitant ED. These are considered the gold-standard for PD treatment and only offered to patients with stable disease.[65]

To date, only one study has assessed the potential benefits of BoNT-A on PD. Muñoz-Rangel et al outlined the use of intralesional injections of 100 units of BoNT-A in 22 patients with stable-phase PD.[66] Within the cohort, 14 patients had <30° of curvature, and the remaining 8 had 30°-60° of curvature. With respect to ED, 19 (86.4%) patients had mild-to-moderate ED, and one (4.5%) patient had severe ED. The primary outcome assessed was degree of curvature, with secondary outcomes of plaque thickness, erectile function, and penile pain. Erectile function was quantified using the International Index of Erectile Function questionnaire, and pain level was quantified using the VAS. The complete results of the study are described in Table 3. Overall, statistically significant improvements were noted in all outcome parameters. Notably, at 16 weeks after treatment, 19 patients had <30° of curvature and 3 had 30°-60° of curvature. In addition, after treatment, 7 (30.8%) patients had normal sexual function, 14 (63.6%) patients had mild-to-moderate ED, and one (4.5%) patient had severe ED. The authors did not report any adverse effects from the BoNT-A therapy. While the results of this study are intriguing, there are serious limitations, namely, a small sample size, a lack of a control group, a relatively short period of follow-up, and only a single administration of BoNT-A, which can be heavily dependent on provider experience in determining the efficacy and safety of administration. The authors hypothesize that the potential role of BoNT-A in the treatment of PD may be related to the toxins' potential effectiveness in the treatment of hypertrophic scars and keloids.[67,68] Although the molecular mechanism of action of BoNT-A in the treatment of these pathologies remains unclear, it is postulated that BoNT-A affects fibroblast proliferation and results in decreased production of transforming growth factor beta 1, a key regulator of wound healing and scarring, and other growth factors.[69,70] Notably, transforming growth factor beta 1 has been demonstrated to be overexpressed in other disorders of wound healing, including Dupuytren's contracture and PD.[71] Unfortunately, these hypotheses are inconsistent in a few ways. First, it should be noted that while there is evidence of BoNT-A effectiveness in the treatment of hypertrophic scars and keloids, there are also *in vitro* and human studies that have failed to demonstrate improvements, mainly in keloid scars, after the use of BoNT-A.[72,73] Moreover, making the assumption that the postulated mechanism of action of BoNT-A is correct, it would be more reasonable to assume that the toxin would potentially be more efficacious in the active-phase of PD, when active fibroblast proliferation and growth factor production is occurring, rather than in the stable phase of the disease when these changes have subsided. In the study by Muñoz-Rangel et al, the patient population consisted of individuals with a stable plaque (>12 months from the onset of illness), indicating likely stable-phase disease.[66] It clear that much more data are necessary before

Table 3. Outcomes of BoNT for the treatment of Peyronie's disease

	Degree of curvature	Thickness of plaque (cm)	Erectile unction (IIEF-5)	Pain (visual analog scale score)
Pretreatment	32.95 ± 9.21°	0.34 ± 0.20	16.18 ± 4.46	3.36 ± 3.48
Posttreatment	25 ± 9.38°	0.27 ± 0.13	18.22 ± 4.55	1.14 ± 1.58
P value	.025	.014	.002	.001

IIEF = International Index of Erectile Function.

any conclusions can be drawn about BoNT-A as a treatment for PD. Future clinical studies should include a control group, treatment of active-phase and stable-phase PD patients, and compare single vs multiple cycles of BoNT-A administration. Furthermore, more investigation into the underlying cellular mechanisms of BoNT-A and its influence on fibroblast proliferation and growth factor expression is needed.

Penile Retraction

Penile retraction occurs when the smooth muscle fibers in the dartos fascia contract, which conceals part of the penis by retracting it inwards. This contraction can be triggered by cold, exercise, or stress. Owing to the appearance of a temporarily shorter than normal flaccid penile length, some men are embarrassed by penile retraction when observed by their sexual partner or other individuals in public changing areas such as locker rooms. Penile retraction may not be a widely recognized concern, but dissatisfaction with flaccid penile length is relevant to many men. In fact, 27% of US men surveyed reported that flaccid penile length was a dissatisfying aspect of their genital self-image.[74] Augmentation of flaccid penile length, through abatement of penile retraction, may be achieved with BoNT-A, which presumably works by paralyzing the smooth muscles in dartos fascia.[75] In a pilot study by Shaeer et al, 10 men with bothersome penile retraction were given intra-dartos injections of 100 units of BoNT-A.[75] After one round of injections, 70% of these men reported a subjective improvement in amplitude and frequency of retraction, as well as overall improved flaccid unstretched length. Objective measurements performed by the authors in clinic revealed only slight improvements in flaccid unstretched penile length (mean of 2.5 mm, 7.5% $P = .0002$) in the baseline state. The application of heat packs, which are intended to suppress the retraction reflex, reported slightly better changes than those observed at the baseline state (mean of 6.9 mm, 15.3% $P = .0001$). The most significant improvements were noted after the application of ice to the genitalia to trigger penile retraction (mean of 11.9 mm, 53.6% $P = .0001$) and through the elicitation of the retraction reflex by scratching the medial groin region with a sterile needle (mean of 11 mm, 40% $P = .00005$). No objective improvements in flaccid outstretched length or erect length were reported. These improvements in the unstretched length peaked at 5 weeks after injection and began to dissipate by 44 to 5 months. Patients reported no changes in penile function, and no adverse effects were reported. The authors of the study acknowledge the discrepancies in improvement between the subjective and objective data. Apart from self-measurement bias, a placebo effect and a lack of standardization in terms of measurement technique and instrumentation used for self-measurement could be some of the reasons for such discrepancies. In addition, the authors point out that the stress associated with in-office clinical examination could potentially trigger more than normal retraction at the time of measurement and also impact the results.

As of now, men seeking to improve flaccid and erect penile length are turning to a variety of options ranging from penile extender devices to more invasive options such as the Penuma implant (Gesiva, Eden Prairie, MN), suprapubic lipectomy, penile disassembly technique, and, most commonly, the release of the suspensory ligaments in combination with an inverted V-Y skin plasty.[76–78] Further investigation into intra-dartos BoNT-A administration may provide a potential avenue for a less invasive therapy in the subset of patients whose main concern is flaccid penile length. Future studies should explore modifications in BoNT-A dosage, frequency of injection administration, and pairing of BoNT-A injections with other therapies such as vacuum devices or penile traction devices. In addition, these studies must attempt to address some of the shortcomings of this pilot study and provide more reliable data including RCTs.

Scrotal Aesthetics

In recent years, the aesthetics of male genitalia has become an area of interest for potential intervention.[79] Patients have demonstrated concerns regarding scrotal size, scrotal skin wrinkling, and even excess scrotal sweating. In an effort to improve these issues, some providers have proposed and treated patients with BoNT. This therapy has been termed *Scrotox*. The outcomes, as explained by these providers, include an enlarged appearance of the scrotum due to relaxation of the cremasteric muscle, decreased scrotal wrinkles from relaxation of dartos muscle, and relief of CSP in those with concurrent complaints of pain. The increased scrotal surface area is also theorized to promote heat loss and reduce sweating in this region. At present, no peer-reviewed literature on the safety and efficacy of these treatments exists on PubMed. It is clear that before any recommendations or clinical application can be considered, more critical data regarding this therapy are necessary.

CONCLUSION

The utilization of BoNT-A in the treatment of male sexual dysfunction represents a relatively new domain of urological research. Based on the current literature available, it is evident that a great deal of RCT data and a much more robust understanding of the potential underlying pathways involved in mediating the effects of BoNT-A are necessary before any further clinical adoption. The current data show mixed outcomes for the treatment of various sexual pathologies but pave the way for future investigation into topics such as more optimal dosing regimens that could improve treatment efficacy, potential roles for other BoNT serotypes in the treatment of male sexual pathology, and the use of combination therapies involving BoNT-A. It should be noted that even if future studies yield more promising results, the realistic clinical utility of BoNT-A for the treatment of any specific male sexual pathology will likely ultimately be predicated on the existing treatment landscape. In the case of pathologies such as ED and PD, which already have a variety of proven therapies, there will be a much higher barrier to

any clinical adoption than for conditions such as CSP and penile retraction, where the existing therapies are ineffective and limited options currently exist. With respect to safety, while many of the studies noted in this review described minimal adverse effects or complications resulting from BoNT-A administration, these were all in the context of immediate or short-term follow-up. Long-term safety data, especially in patients with repeated administration, are necessary; however, they will likely not be available for the foreseeable future, and this should be communicated to patients before any BoNT-A therapy. Overall, BoNT-A is an intriguing and often used therapy in modern clinical medicine. However, its role in the treatment of male sexual pathology remains highly variable at this time and will likely depend on the findings of future studies.

Corresponding Author: Wayne J. G. Hellstrom, MD, Department of Urology, Tulane University School of Medicine, 1430 Tulane Avenue 86-42, New Orleans, USA. Tel: +1 504 988 3361; E-mail: whellst@tulane.edu

Conflict of Interest: The authors report no conflicts of interest.

Funding: None.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Amit G. Reddy; Brian P. Dick; Wayne J.G. Hellstrom

(b) Acquisition of Data
Amit G. Reddy; Brian P. Dick; Caleb Natale; Kole P. Akula

(c) Analysis and Interpretation of Data
Amit G. Reddy; Brian P. Dick; Caleb Natale; Kole P. Akula; Ayad Yousif

Category 2

(a) Drafting the Article
Amit G. Reddy; Brian P. Dick; Caleb Natale; Kole P. Akula

(b) Revising It for Intellectual Content
Amit G. Reddy; Ayad Yousif; Wayne J.G. Hellstrom

Category 3

(a) Final Approval of the Completed Article
Amit G. Reddy; Brian P. Dick; Caleb Natale; Kole P. Akula; Ayad Yousif; Wayne J.G. Hellstrom

REFERENCES

1. van Ermengem E. Classics in infectious diseases. A new anaerobic bacillus and its relation to botulism. E. van Ermengem. Originally published as "Ueber einen neuen anaeroben Bacillus und seine Beziehungen zum Botulismus" in Zeitschrift Fur Hygiene und Infektionskrankheiten 26: 1-56, 1897. **Rev Infect Dis 1979;1:701-719**.
2. Kerner J. Vergiftung durch verdorbene Würste. **Tübinger Blätter für Naturwissenschaften und Arzneykunde 1817; 3:25**.
3. Scott AB. Botulinum toxin injection of eye muscles to correct strabismus. **Trans Am Ophthalmological Soc 1981; 79:734-770**.
4. Chen S. Clinical uses of botulinum neurotoxins: current indications, limitations and future developments. **Toxins 2012; 4:913-939**.
5. Simpson LL. Molecular pharmacology of botulinum toxin and tetanus toxin. **Annu Rev Pharmacol Toxicol 1986; 26:427-453**.
6. Stupak HD, Maas CS. New procedures in facial plastic surgery using botulinum toxin A. **Facial Plast Surg Clin North Am 2003;11:515-520**.
7. Dutta SR, Passi D, Singh M, et al. Botulinum toxin the poison that heals: a brief review. **Natl J Maxill Surg 2016;7:10-16**.
8. Jankovic J, Brin MF. Botulinum toxin: historical perspective and potential new indications. **Muscle Nerve Suppl 1997; 6:S129-S145**.
9. Sadick NS. The cosmetic use of botulinum toxin type B in the upper face. **Clin Dermatol 2004;22:29-33**.
10. Pirazzini M, Rossetto O, Eleopra R, et al. Botulinum neurotoxins: Biology, pharmacology, and Toxicology. **Pharmacol Rev 2017;69:200-235**.
11. Brin MF, Blitzer A. Botulinum toxin: dangerous terminology errors. **J R Soc Med 1993;86:493-494**.
12. Peyronnet B, Gamé X, Vurture G, et al. Botulinum toxin Use in Neurourology. **Rev Urol 2018;20:84-93**.
13. Dolly JO. Therapeutic and research exploitation of botulinum neurotoxins. **Eur J Neurol 1997;4:S5-S9**.
14. Montecucco C, Schiavo G. Mechanism of action of tetanus and botulinum neurotoxins. **Mol Microbiol 1994;13:1-8**.
15. Dressler D, Adib Saberi F. Botulinum toxin: mechanisms of action. **Eur Neurol 2005;53:3-9**.
16. Hayashi T, McMahon H, Yamasaki S, et al. Synaptic vesicle membrane fusion complex: action of clostridial neurotoxins on assembly. **EMBO J 1994;13:5051-5061**.
17. Südhof TC, Rizo J. Synaptic vesicle exocytosis. **Cold Spring Harbor Perspect Biol 2011;3**.
18. Nigam PK, Nigam A. Botulinum toxin. **Indian J Dermatol 2010;55:8-14**.
19. Samizadeh S, De Boulle K. Botulinum neurotoxin formulations: overcoming the confusion. **Clin Cosmet Investig Dermatol 2018;11:273-287**.
20. Administration USFaD. Botox label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf. Accessed September 21, 2019. Published 1989. Revised April 2017.
21. Crowner BE, Torres-Russotto D, Carter AR, et al. Systemic weakness after therapeutic injections of botulinum toxin a: a case series and review of the literature. **Clin neuropharmacology 2010;33:243-247**.
22. Baizabal-Carvallo JF, Jankovic J, Pappert E. Flu-like symptoms following botulinum toxin therapy. **Toxicon 2011;58:1-7**.

23. Wyndaele JJ, Van Dromme SA. Muscular weakness as side effect of botulinum toxin injection for neurogenic detrusor overactivity. **Spinal cord 2002;40:599.**
24. Botox label. U.S. Food and drug administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf. Accessed September 21, 2019. Published 1989. Revised April 2017.
25. Naumann M, Jankovic J. Safety of botulinum toxin type A: a systematic review and meta-analysis. **Curr Med Res Opin 2004;20:981-990.**
26. Davis BE, Noble MJ, Weigel JW, et al. Analysis and management of chronic testicular pain. **J Urol 1990;143:936-939.**
27. Nickel JC, Siemens DR, Nickel KR, et al. The patient with chronic epididymitis: characterization of an enigmatic syndrome. **J Urol 2002;167:1701-1704.**
28. Wesselmann U, Burnett AL, Heinberg LJ. The urogenital and rectal pain syndromes. **Pain 1997;73:269-294.**
29. Strebel RT, Leippold T, Luginbuehl T, et al. Chronic scrotal pain syndrome: management among urologists in Switzerland. **Eur Urol 2005;47:812-816.**
30. Ciftci H, Savas M, Yeni E, et al. Chronic orchialgia and associated diseases. **Curr Urol 2010;4:67-70.**
31. Calixte N, Brahmbhatt J, Parekattil S. Chronic testicular and groin pain: pathway to relief. **Curr Urol Rep 2017;18:83.**
32. Keoghane SR, Sullivan ME. Investigating and managing chronic scrotal pain. **Bmj 2010;341:c6716.**
33. Levine L. Chronic orchialgia: evaluation and discussion of treatment options. **Ther Adv Urol 2010;2:209-214.**
34. Starke NR, Costabile RA. Medical management of chronic orchialgia. **Translational Androl Urol 2017;6(Suppl 1):S48-S50.**
35. Khambati A, Lau S, Gordon A, et al. OnabotulinumtoxinA (Botox) nerve blocks provide durable pain relief for men with chronic scrotal pain: a pilot Open-label trial. **J Sex Med 2014;11:3072-3077.**
36. Tojuola B, Layman J, Kartal I, et al. Chronic orchialgia: review of treatments old and new. **Indian J Urol 2016;32:21-26.**
37. McCabe MP, Sharlip ID, Atalla E, et al. Definitions of sexual dysfunctions in Women and men: a Consensus Statement from the Fourth International Consultation on sexual medicine 2015. **J Sex Med 2016;13:135-143.**
38. Dick B, Reddy A, Gabrielson AT, et al. Organic and Psychogenic causes of sexual dysfunction in Young men. **Int J Med Rev 2018;4:102-111.**
39. Waldinger MD. The neurobiological approach to premature ejaculation. **J Urol 2002;168:2359-2367.**
40. Waldinger MD. Premature ejaculation: Advantages of a new classification for understanding etiology and prevalence rates. **Sexologies 2008;17:30-35.**
41. Serefoglu EC, Silay MS. Botulinum toxin-A injection may be beneficial in the treatment of life-long premature ejaculation. **Med Hypotheses 2010;74:83-84.**
42. Serefoglu EC, Hawley WR, Lasker GF, et al. Effect of botulinum-A toxin injection into bulbospongiosus muscle on ejaculation latency in male rats. **J Sex Med 2014;11:1657-1663.**
43. Ongun S, Acar S, Koca P, et al. Can botulinum-A toxin Be used to delay ejaculation: results of an ejaculation model in male rats. **J Sex Med 2019;16:1338-1343.**
44. Li ZT, Li YF, Zhang Y, et al. [Injection of botulinum-A toxin into bulbospongiosus muscle for primary premature ejaculation: a preliminary clinical study]. **Zhonghua Nan Ke Xue 2018;24:713-718.**
45. Abdel-Meguid TA, Alsayyad AJ, Tayib AM, et al. Can intraprostatic injection of OnabotulinumtoxinA be Benefi cial to treat premature ejaculation? Results of a prospective study. **J King Abdulaziz University-Medical Sci 2017;24:1-7.**
46. Bartoletti R, Cai T, Mondaini N, et al. Prevalence, incidence estimation, risk factors and characterization of chronic prostatitis/chronic pelvic pain syndrome in urological hospital outpatients in Italy: results of a multicenter case-control observational study. **J Urol 2007;178:2411-2415 [discussion: 2415].**
47. Screponi E, Carosa E, Di Stasi SM, et al. Prevalence of chronic prostatitis in men with premature ejaculation. **Urology 2001;58:198-202.**
48. El-Enen MA, Abou-Farha M, El-Abd A, et al. Intraprostatic injection of botulinum toxin-A in patients with refractory chronic pelvic pain syndrome: the transurethral vs. transrectal approach. **Arab J Urol 2015;13:94-99.**
49. Falahatkar S, Shahab E, Gholamjani Moghaddam K, et al. Transurethral intraprostatic injection of botulinum neurotoxin type A for the treatment of chronic prostatitis/chronic pelvic pain syndrome: results of a prospective pilot double-blind and randomized placebo-controlled study. **BJU Int 2015;116:641-649.**
50. Do TP, Hvedstrup J, Schytz HW. Botulinum toxin: a review of the mode of action in migraine. **Acta Neurol Scand 2018;137:442-451.**
51. Bach-Rojecky L, Dominis M, Lackovic Z. Lack of anti-inflammatory effect of botulinum toxin type A in experimental models of inflammation. **Fundam Clin Pharmacol 2008;22:503-509.**
52. Gaxiola GM, Aguilar IE, Paz GP. Method for treating premature ejaculation with a botulinum neurotoxin. In: Google Patents. 2012. https://patents.google.com/patent/US8329193. Accessed June 29, 2020.
53. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. **Urol Clin North Am 2005;32:379-395. v.**
54. Gandaglia G, Briganti A, Jackson G, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. **Eur Urol 2014;65:968-978.**
55. Yafi FA, Jenkins L, Albersen M, et al. Erectile dysfunction. **Nat Rev Dis primers 2016;2:16003.**
56. Kessler A, Sollie S, Challacombe B, et al. The global prevalence of erectile dysfunction: a review. BJU Int, https://doi.org/10.1111/bju.14813. E-pub ahead of print.

57. Reddy AG, Alzweri LM, Gabrielson AT, et al. Role of penile prosthesis in priapism: a review. **World J men's Health 2018; 36:4-14.**
58. Ghanem H, Raheem AA, AbdelRahman IFS, et al. Botulinum neurotoxin and its potential role in the treatment of erectile dysfunction. **Sex Med Rev 2018;6:135-142.**
59. De Young L, Campbell J, Radomski S, et al. 142 intracavernosal injection of botulinum toxin to improve erectile function in older rats. **J Sex Med 2017;14(Supplement 1):S40-S41.**
60. Hellstrom WJG. Medical management of Peyronie's disease. **J Androl 2009;30:397-405.**
61. Al-Thakafi S, Al-Hathal N. Peyronie's disease: a literature review on epidemiology, genetics, pathophysiology, diagnosis and work-up. **Translational Androl Urol 2016;5:280-289.**
62. Bilgutay AN, Pastuszak AW. PEYRONIE'S disease: a review OF etiology, DIAGNOSIS, and management. **Curr Sex Health Rep 2015;7:117-131.**
63. Bjekic MD, Vlajinac HD, Sipetic SB, et al. Risk factors for Peyronie's disease: a case-control study. **BJU Int 2006; 97:570-574.**
64. Nehra A, Alterowitz R, Culkin DJ, et al. Peyronie's disease: AUA Guideline. **J Urol 2015;194:745-753.**
65. Levine LA, Larsen SM. Surgery for Peyronie's disease. **Asian J Androl 2013;15:27-34.**
66. Munoz-Rangel CA, Fernandez-Vivar E, Banuelos-Gallo RA, et al. Minimally invasive therapy using intralesional OnabotulinumtoxinA in Peyronie's disease. **Urol J 2015;12:2105-2110.**
67. Fanous A, Bezdjian A, Caglar D, et al. Treatment of keloid scars with botulinum toxin type A versus Triamcinolone in an Athymic Nude Mouse model. **Plast Reconstr Surg 2019; 143:760-767.**
68. Elhefnawy AM. Assessment of intralesional injection of botulinum toxin type A injection for hypertrophic scars. **Indian J Dermatol Venereol Leprol 2016;82:279-283.**
69. Lee B-J, Jeong J-H, Wang S-G, et al. Effect of botulinum toxin type a on a rat surgical wound model. **Clin Exp Otorhinolaryngol 2009;2:20-27.**
70. Austin E, Koo E, Jagdeo J. The cellular response of keloids and hypertrophic scars to botulinum toxin A: a Comprehensive literature review. **Dermatol Surg 2018;44:149-157.**
71. El-Sakka AI, Hassoba HM, Pillarisetty RJ, et al. Peyronie's disease is associated with an increase in transforming growth factor-beta protein expression. **J Urol 1997;158:1391-1394.**
72. Gauglitz GG, Bureik D, Dombrowski Y, et al. Botulinum toxin A for the treatment of keloids. **Skin Pharmacol Physiol 2012; 25:313-318.**
73. Haubner F, Leyh M, Ohmann E, et al. Effects of botulinum toxin A on patient-specific keloid fibroblasts in vitro. **Laryngoscope 2014;124:1344-1351.**
74. Gaither TW, Allen IE, Osterberg EC, et al. Characterization of genital dissatisfaction in a National sample of U.S. Men. **Arch Sex Behav 2017;46:2123-2130.**
75. Shaeer O, Shaeer K, Shaeer A. Botulinum toxin a (Botox) for relieving penile retraction. **J Sex Med 2009;6:2788-2794.**
76. Perovic SV, Djordjevic MLJ. Penile lengthening. **BJU Int 2000; 86:1028-1033.**
77. Shaeer O, Shaeer K, el-Sebaie A. Minimizing the losses in penile lengthening: "V-Y half-skin half-fat advancement flap" and "T-closure" combined with severing the suspensory ligament. **J Sex Med 2006;3:155-160.**
78. Nikoobakht M, Shahnazari A, Rezaeidanesh M, et al. Effect of penile-extender device in increasing penile size in men with shortened penis: preliminary results. **J Sex Med 2011; 8:3188-3192.**
79. Cohen PR. Scrotal Rejuvenation. **Cureus 2018;10:e2316.**