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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Injectable Botulinum Toxin for Pelvic Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	August 22, 2019
Report Length:	30 Pages

CADTH

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Cite As: Injectable Botulinum Toxin for pelvic pain: a review of clinical effectiveness, cost-effectiveness, and guidelines. Ottawa: CADTH; 2019 Aug. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

BTA	botulinum toxin A (onabotulinum toxin A)
RCT	randomized controlled trial
SR	systematic review
VAS	visual analogue scale

Context and Policy Issues

Gynecological conditions of the pelvic floor region can include vulvodynia (vulvar pain lasting at least 3 months with no identifiable cause),[1] vaginismus (or genito-pelvic pain or penetration disorder, the inability to achieve non-painful vaginal penetration of any kind),[2] endometriosis (in which cells of the endometrium grows outside of the uterus), and provoked vestibulodynia (localized pain in the vulvar vestibule caused by physical contact).[3] Gynecological conditions of the pelvic floor region are generally considered to occur as a result of a multifactorial process that includes genetics, hormonal changes, inflammation, musculoskeletal issues (such as hypertonic muscles), neurologic mechanisms, psychosocial factors (often related to sexual functioning), and structural issues (such as perineal descent), but etiologies are often unknown.[1,4,5] First-line treatments for these conditions include physiotherapy, dilation therapy, sex counseling, psychotherapy, or a combination of therapies.[2,6] Increasingly, botulinum toxin has become an alternative therapy option for individuals with pelvic pain.[6]

Botulinum toxin is a toxin produced by the *Clostridium* bacteria.[6] Botulinum toxin is used in neuromuscular disorders, ophthalmic disorders, chronic pain, cosmetic and dermatological applications, pelvic floor disorders, gastrointestinal disorders, and spasticity.[6] In pelvic pain, it is typically injected into the muscle, where it inhibits release of acetylcholine, causing blockage of muscle spasms.[6]

Pelvic pain disorders can affect an individual's feelings of self worth, quality of life, sexual functioning, psychological well being, and relationships.[1-3] According to a 2017 cross-sectional study, the average hospital-associated cost of chronic pelvic pain (pelvic and perineal pain, dysmenorrhea, or dyspareunia) in Canada amounted to C$25 million per year between 2008 and 2012.[7] Many cases of pelvic pain go undiagnosed, as patients often do not report sexual dysfunction, and it has been reported that patients with vulvodynia had the condition for an average of 7 years before seeking help.[2,3] Additionally, as vulvodynia is not well understood, individuals with the condition may wait an average of 5 years to receive a diagnosis after seeking treatment.[3]

There is uncertainty regarding the of effectiveness of botulinum toxin for some chronic pelvic pain conditions. The purpose of this report is to evaluate the evidence regarding the clinical effectiveness and safety of botulinum toxin compared with other treatments or placebo for patients with chronic pelvic floor dysfunction and pain. Evidence regarding the cost-effectiveness of botulinum toxin for pelvic pain was also sought to support decision making. Evidence-based recommendations were sought to provide guidance on the use of botulinum toxin for these conditions.

Research Questions

1. What is the clinical effectiveness of injectable botulinum toxin for pelvic floor pain?
2. What is the cost-effectiveness of injectable botulinum toxin for pelvic floor pain?
3. What are the evidence-based guidelines regarding injectable botulinum toxin for pelvic floor pain?

Key Findings

Two systematic reviews and three randomized controlled trials provided evidence on the clinical effectiveness of injectable botulinum toxin for pelvic floor pain. Two systematic reviews were identified regarding the clinical effectiveness of botulinum toxin type A injections for pelvic floor pain (female sexual pain and vaginismus). Botulinum toxin type A injections appeared to have no effect on pain, sexual functioning, or quality of life when compared to placebo. One systematic review included one study examining botulinum toxin compared with placebo; 100% of patients (n = 8) treated with botulinum toxin injection achieved successful intercourse compared with 0% (n = 5) of patients treated with placebo.

Evidence from two randomized controlled trials comparing botulinum toxin A injections with placebo for patients with myofascial pelvic pain or provoked vestibulodynia showed no difference between groups in pain reduction. One RCT provided physiotherapy for both placebo and intervention groups after four weeks in patients with myofascial pelvic pain; there were no differences in pain or sexual functioning between the groups who received botulinum injection and physiotherapy and placebo and physiotherapy. A third randomized controlled trial reported that physiotherapy was more effective than injections of botulinum toxin type A in patients with vaginismus for female sexual functioning index components and success of sexual intercourse.

No evidence regarding the cost-effectiveness of botulinum toxin, and no guidelines or recommendations regarding injectable botulinum toxin for pelvic floor pain, were identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were botulinum toxin and pelvic floor pain. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and July 20, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed

for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with female genitalia or a uterus with pelvic floor pain (e.g., vulvodynia, vaginismus, endometriosis, short pelvic floor syndrome), not including bladder conditions
Intervention	Injectable botulinum toxin, either alone or in combination with another treatment (e.g., dilation, physiotherapy, myofascial release, biofeedback)
Comparator	Other treatments for pelvic pain; placebo
Outcomes	Q1: Clinical effectiveness (e.g., changes in pain, adverse events, completion of sexual intercourse) Q2: Cost-effectiveness (e.g., incremental cost-effectiveness ratio, incremental cost per effectiveness gain) Q3: Guidelines (e.g., guidelines regarding where or how the procedure should be done, guidelines regarding modalities that should be used during the procedure [e.g., Computed tomography or magnetic resonance imaging])
Study Designs	Systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised by one reviewer using a Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2),[8] and randomized studies were critically appraised using the Down's and Black checklist.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 134 citations were identified in the literature search. Following screening of titles and abstracts, 113 citations were excluded and 21 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 18 publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised two SRs, and three randomized controlled trials (RCTs). Appendix 1 presents the PRISMA[10] flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Two included studies were SRs[11,12] (one with a meta-analysis).[12] The SRs were published in 2019[11] and 2018.[12] The date ranges for the searches for the SRs were up to February 25, 2016[11] and April, 30 2018.[12] The inclusion criteria for both SRs were broader than those of the current report; however, one SR included five studies relevant to this report,[11] and the other included six studies relevant to this report.[12] All study designs were eligible for inclusion in both SRs, and two primary studies were included in both SRs (Appendix 5 illustrates the overlap between included SRs). Of these two common studies, only one provided relevant results for this report.

Three relevant RCTs were identified.[13-15] One was a double-blinded, placebo controlled trial,[13] one was a double-blinded, placebo controlled trial with an additional unblinded exploratory analysis,[14] and one was a parallel design RCT.[15]

Country of Origin

The included SRs were published by first authors from the United States[11] and Italy.[12] The included RCTs were conducted in Switzerland[13,14] and Iran.[15]

Patient Population

The patient population for one SR was patients with female sexual dysfunction, which included hypoactive sexual desire disorder, arousal disorder, orgasmic disorder, and sexual pain disorder.[11] From this SR, patients with sexual pain disorder were of relevance to this report. The second SR included patients with a diagnosis of vaginismus.[12]

In the primary studies, all included patients were adults, either 18 years or older,[13,14] or between the ages of 20 and 40.[15] One RCT included patients with persistent myofascial pain rated at a six or higher on the visual analog scale (VAS, 10 cm). One RCT included patients with provoked vestibulodynia, not on concurrent therapy for the condition, who were taking or using contraception.[14] The final RCT included patients diagnosed with severe primary vaginismus rated at a level of III or IV on the Lamont scale.[15]

Interventions and Comparators

All studies examined botulinum toxin type A (BTA, or onabotulinum toxin A) injections as the primary intervention.[11-15]

The SRs had broader inclusion criteria than the inclusion criteria of this report. One SR included “various treatments”[11] and the other included any therapeutic intervention (e.g., behavioral therapy, including systematic desensitization, sensate focusing, Kegel and Paula Garburg’s muscle exercises and muscle relaxation, pharmacological treatment [local botulinum toxin or intravenous diazepam], and pelvic floor physiotherapy[12]).

The RCTs examined varying doses of BTA and varying injection sites. In one RCT, 200 units in 20 mL saline were injected bilaterally into areas that were reported to have pain (and after 4 weeks, 8 weeks of physiotherapy was provided to both placebo and BTA groups).[13] In another RCT there were two intervention study arms: 50 units in 1 mL saline were injected bilaterally into subcutaneous layers of the dorsal vestibulum (0.5 mL per side) or 100 units in 1 mL bilaterally (0.5 mL per side).[14] In the last RCT, 500 units in 1.5 cc of saline were injected into three points bilaterally in the levator ani muscles.[15] Comparators for the included SRs were all comparators (including placebo, no comparator, and no treatment)[11] and no treatment (including placebo and control).[12]

The comparators for the included RCTs were placebo (saline injections),[13,14] and physiotherapy (including relaxation exercises, functional electric stimulation [FES], desensitization, and sensation focus) for 12 weeks.[15]

Outcomes

One included SR examined changes in the female sexual function index, pain (10 cm VAS), female sexual distress scale, and the female intervention efficacy index.[11] The other included SR included studies examining the outcome of "successful intercourse", but the specific definition of this was not provided.[12]

The included RCTs examined changes in pain symptoms,[13-15] including with the VAS 10cm,[13,14] von Frey filaments,[14] Marinoff dyspareunia scale (0 to 3),[14] and the Female Sexual Function Index.[15] Additional outcomes included successful intercourse,[15] frequency of sexual intercourse,[14] quality of life,[13] the pelvic floor distress inventory (PFDI),[13] and treatment success (a greater than or equal to 2-point improvement on cotton swab VAS [pain on depression of skin with Q-tip or cotton bud], or reported symptom free).[14]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

Both included SRs had a comprehensive search strategy using multiple databases.[11,12] One SR conducted the search in 2016, but published the review in 2019. This delay may have affected the relevance of the publication, as publications between 2016 and 2019 would have not been considered for inclusion.[11] Both SRs also used two or more reviewers for study selection (with one SR performing it in triplicate[11]). Conflicts of interest were reported for both SRs,[11,12] with one SR reporting no conflicts of interest.[12] Both studies were not industry-funded.[11,12] One study included an *a priori* protocol, specified the procedure for data extraction, and assessed the quality of included studies.[12]

Limitations of the included SRs included unclear interventions and comparators that were eligible for inclusion.[11] This lack of clarity made it difficult to determine whether the inclusion criteria were broad or specific, and made it difficult to determine whether the reviews were comprehensive reviews of all possible comparators.[11] Additionally, many study details were not reported, such as reason for receipt of BTA injections (e.g., what conditions the patients had) so specific conclusions about the effectiveness of BTA for some conditions was not possible.[11,12] Some potentially relevant outcomes (such as quality of life or pain reduction) were not reported in the SRs.[11,12]

One SR conducted a meta-analysis.[12] The meta-analysis included all identified interventions (i.e., pharmacotherapies, behavioral therapies, other therapies) and comparators (i.e., no comparator, placebo, no treatment, other treatment) together in the analysis, which resulted in extremely high and significant heterogeneity ($I^2 = 68.59$), and was likely not clinically appropriate.[12] This meta-analysis may provide some insight regarding the effectiveness of "any treatment" versus "no treatment", however did not allow for determination of the true magnitude of effect for any given treatment. Although a sensitivity analysis appeared to have been performed for the effectiveness of BTA compared to placebo or no treatment only, the data for this analysis were not provided, and studies were combined that had different doses and comparators.[12]

Randomized Controlled Trials

All included RCTs reported clear aims and objectives.[13-15] The randomization procedures and statistical tests were all appropriate, and the interventions and comparators were clear, with the full procedures, doses, and injection sites described.[13-15] Outcome measurements were clear, and validated tools such as the VAS and Wong-Baker FACES Pain Rating Scale were used to assess outcomes.[13-15]

Generalizability and external validity may be a limitation of the included RCTs. One RCT included patients from a university setting who were highly educated,[15] one RCT included patients who had undergone other treatments previously without success,[14] and one RCT included patients with severe pain, with a majority of patients also having other pain disorders.[13] These populations were very specific, and therefore may not reflect average patients with pelvic floor pain disorders. Despite this, all patients were recruited from the same population for both controls and interventions within each study, increasing internal validity for those populations.

Power calculations were performed for all studies,[13-15] but one RCT had unequal allocation into study arms, with one arm not recruiting enough participants to reach the targeted minimum sample size. It is unknown whether this smaller number limited the power to detect significant differences.[14]

Two RCTs blinded the participants and the physicians administering the treatments.[13,14] This may assist in mitigating bias during assessments of outcomes by both the participant (self-reported pain) and physician. One study did not blind participants, but this was likely to not have been feasible as the comparator and intervention were substantially different from one another (i.e., BTA injection and physiotherapy).[15] The majority of outcomes were self-reported (e.g., sexual functioning, success of intercourse) which may be subject to recall bias from participants.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Botulinum Toxin for Pelvic Floor Pain

Systematic Reviews and Meta-analyses

The first SR by Weinberger et al[11] included five studies examining BTA injection to treat female sexual dysfunction. Of these five studies, three did not have any comparator, and therefore were not eligible for this report. The two eligible studies examined the effectiveness of BTA compared with other treatment ("conventional therapy") and BTA compared with placebo.[11] Women who received BTA had a mean pain decrease (mean VAS) from 7.44 to 5.14 and women receiving placebo had a mean VAS decrease from 7.63 to 5.13 (both $P < 0.001$).[11] Between-group differences were not compared statistically, but the authors concluded that compared with placebo, BTA appeared to have no impact on pain, female sexual functioning, or quality of life.[11] In the study of BTA compared with "conventional therapy", six women succeeded with intercourse on conventional therapy, and six failed.[11] These six failures then received BTA injections, and five (83.3%) of the individuals within this group succeeded with sexual intercourse. There were no direct comparative results reported, and the two groups were likely not comparable as one was refractory to conventional treatment and the other was not. The definition of "conventional therapy" was not specified.[11]

The second SR by Maseroli et al[12] included six studies examining BTA injection to treat vaginismus. Two included studies were also included in the SR by Weinberger et al.,[11] and only one of these studies provided relevant results to this report (i.e., the comparison of BTA versus "conventional therapy", already described).[12] No additional information was provided regarding this study in the Maseroli et al.[12] Three studies had no treatment comparator and were ineligible for this report. The last study examined 25 units of BTA in bulbospongiosus muscle compared with saline injection in patients with primary vaginismus. The study found a 100% success rate with BTA injection (n = 8) and a 0% success rate with placebo (n = 5), but between-group differences were not compared statistically.[12]

Primary Studies – BTA vs. Placebo, BTA and Physiotherapy vs. Placebo and Physiotherapy

Two RCTs compared BTA to placebo.[13,14] One RCT examined patients with myofascial pelvic pain and compared 200-unit injections of BTA bilaterally into reported pain areas to placebo injections. The patients in both placebo and BTA groups then received eight weeks of physiotherapy four week post-injection. Therefore, all time points after four weeks included physiotherapy.[13] The authors found no significant difference in median pain changes (using the Wong-Baker faces pain rating scale) between BTA and placebo, with the exception of a follow-up time of 2 weeks in the left coccygeus muscle (P = 0.046, in favour of placebo).[13] This was the only significant difference out of a total of 36 comparisons (six muscle groups on the each of the left and right sides [coccygeus, iliococcygeus, obturator onternus, piriformus pubcoccygeus, and puborectalis] assessed at three different time points).[13] There were no differences in pelvic function distress inventory scores between the groups (except at 2 weeks, P = 0.01, in favour of placebo), and there were no significant differences between groups in median pelvic organ prolapse distress inventory scores, median colorectal-anal distress inventory scores, or median pain urgency frequency scores.[13] Patients reported no difference between BTA and placebo in median pain scores (VAS) except at 2 weeks (P = 0.045, in favour of BTA).[13] No significant differences were reported between BTA with eight weeks of physiotherapy and placebo with eight weeks of physiotherapy.[13]The authors reported numerically similar adverse events (constipation, urinary incontinence, recurrent urinary tract infection, fecal incontinence, and urinary retention) between BTA and placebo groups.[13]

Another RCT[14] examined patients with provoked vestibulodynia who received an injection of BTA (50 or 100 units) or placebo into the subcutaneous layers of the dorsal vestibulum. From 0 to three months follow-up, no significant differences were found between placebo and BTA (50 unit or 100 unit) for cotton swab provoked pain, von Frey filaments, or Marinoff dyspareunia scales. There were no significant differences in frequency of intercourse between or within the groups. There were also no differences in pain or frequency of intercourse between groups of patients treated with 50 units or 100 units of BTA.[14] No serious adverse events were reported.[14]

Primary Studies – BTA vs. Physiotherapy

The final RCT included patients with severe vaginismus, and compared treatment with 500 units of BTA (injected) versus physiotherapy.[15] When comparing physiotherapy and BTA, there was a significant difference in the number of patients achieving successful intercourse, favouring physiotherapy (P = 0.014). There were significant mean differences in female sexual functioning index components, including desire, arousal, lubrication, orgasm, satisfaction, and pain (all $P \leq 0.005$), in favour of physiotherapy.[15]

Cost-Effectiveness of Botulinum Toxin for Pelvic Floor Pain

No relevant evidence regarding the cost-effectiveness of BTA injections for chronic pelvic floor pain was identified; therefore, no summary can be provided.

Guidelines

No relevant guidelines regarding BTA injections for chronic pelvic floor pain were identified; therefore, no summary can be provided.

Limitations

A limitation of the included literature was the lack of Canadian-specific studies, which limits generalizability of the studies to the Canadian context. The populations included in this review may not accurately reflect a Canadian population, especially as quality of life and psychological aspects of sexual dysfunction may be affected by societal and cultural expectations.[16] Additionally, culture may affect which individuals are likely to seek help for sexual conditions, and from whom.[16]

Furthermore, the meta-analysis[12] had a specific outcome of "completion of sexual intercourse" which may not be an adequate reflection of improvement for many patients, and may have eliminated several eligible studies from the SR. As sexual function and pelvic floor dysfunction are multi-factorial conditions, many of the included studies with strict outcomes of "pain reduction" or "successful intercourse" may miss nuances that are present in determining whether patients feel satisfied with treatment or with their sexual experiences. The included studies also included patients with limited conditions (provoked vestibulodynia, vaginismus, and myofascial pelvic pain), so conclusions regarding the use of BTA in patients with other types of pelvic floor dysfunction such as endometriosis were not possible.

Despite the identification of relevant studies for inclusion in the SRs and the present review, not all studies within the SRs had appropriate comparator groups, and the majority were uncontrolled studies. A previous meta-analysis[17] found that in pharmacological treatments for female sexual dysfunction, the placebo effect may account for 67.7% of treatment effect, so the inclusion of a placebo group or comparator may assist in quantifying how much of an effect the injection alone may have, and assist in accuracy of results. One guideline was identified discussing the use of BTA in chronic pelvic pain,[18] but did not include recommendations for the conditions relevant to this report. This may limit the conclusions that can be made from this review, as these studies could not be included in the results.

Finally, no relevant studies were identified regarding cost-effectiveness of BTA in patients with chronic pelvic floor dysfunction. Therefore, no conclusions can be made regarding the cost-effectiveness of BTA in this population.

Conclusions and Implications for Decision or Policy Making

Two SRs[11,12] and three RCTs[13-15] were identified regarding the use of varying doses of BTA for pelvic floor pain. The conditions studied were female sexual pain dysfunction,[11] vaginismus,[12,15] provoked vestibulodynia[14] and myofascial pelvic pain.[13]

BTA did not significantly reduce pain in patients with myofascial pain or provoked vestibulodynia when compared to placebo (saline) injections. There was a significant placebo effect in both studies. When a combined therapy of BTA and physiotherapy was

compared with a combined therapy of placebo and physiotherapy, no significant differences were found for outcomes such as pain or sexual functioning. When compared directly to physiotherapy alone, BTA alone was not as effective in treating sexual functioning, including successful intercourse, desire, arousal, lubrication, orgasm, satisfaction, and pain.

Further research addressing other conditions of pelvic floor dysfunction, such as endometriosis, and further research including relevant comparators such as placebo or other treatments for pelvic floor dysfunction may reduce uncertainty in the results and assist in determining the role of BTA in the treatment paradigm for pelvic floor dysfunction.

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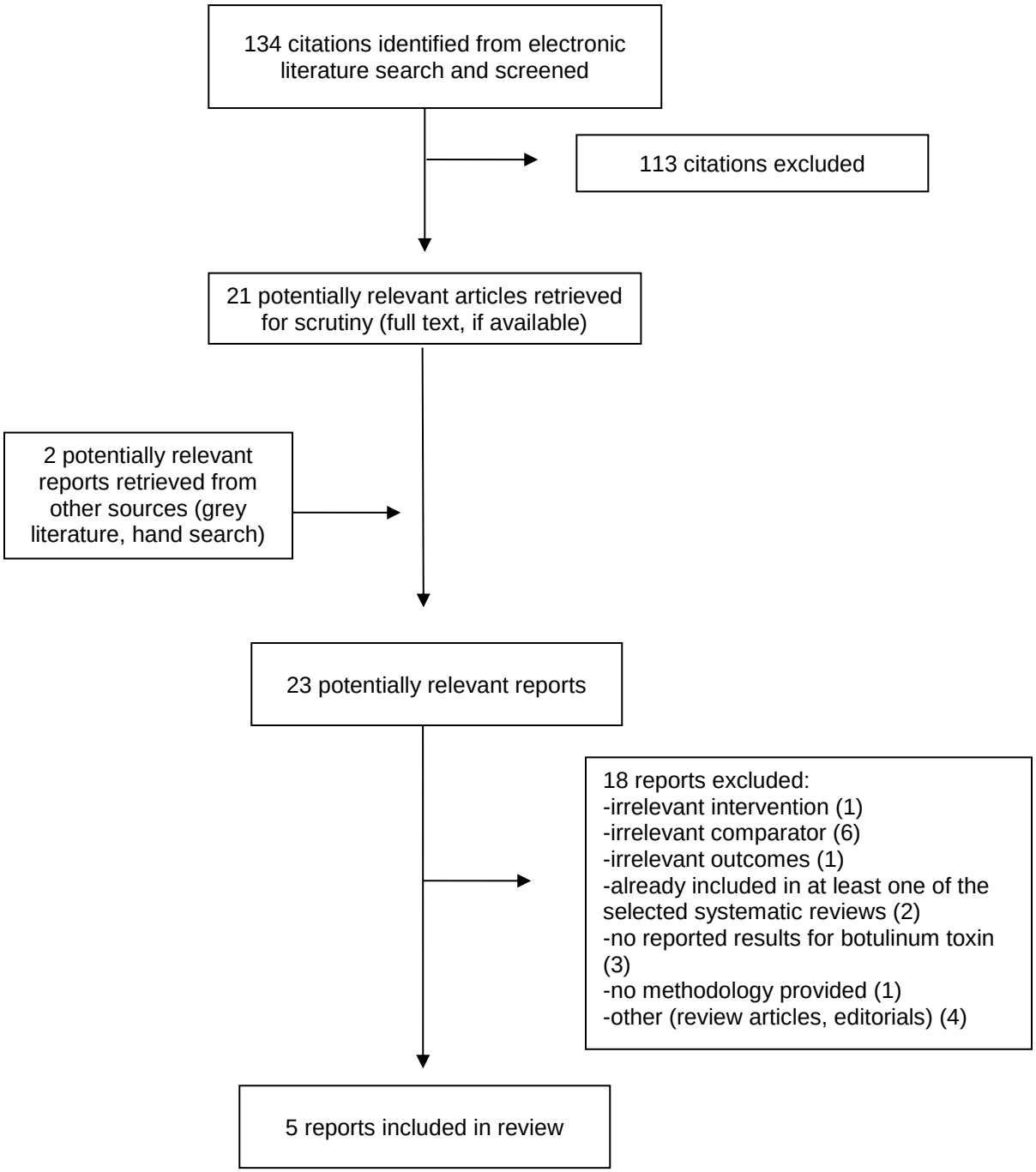
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country, Funding	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
Weinberger 2019[11] **USA** Funding: None	SRs, RCTs and prospective or retrospective cohort studies Number of studies related to particular interventions: 56 Medication 36 Psychotherapeutic 3 Homeopathic 8 Other 5 studies related to BTA	Patients with female sexual dysfunction (i.e., hypoactive sexual desire disorder, arousal disorder, orgasmic disorder, and sexual pain disorder)	*Intervention:* "Various treatments" *Comparator:* Not reported in methods, appears that all comparators (including placebo and no comparator) were eligible	• Female Sexual Function Index • Pain (VAS) • Female Sexual Distress Scale • Female Intervention Efficacy Index
Maseroli 2018[12] **Italy** Funding: None	All study designs (observational and RCT) 3 RCTs 43 Observational studies 6 observational studies related to BTA (five prospective, one retrospective)	Patients with a diagnosis of vaginismus	*Intervention:* Any therapeutic intervention (e.g., behavioral therapy, including systematic desensitization, sensate focusing, Kegel and Paula Garburg's muscle exercises and muscle relaxation, pharmacological treatment [local botulinum toxin, or intravenous diazepam], pelvic floor physiotherapy) *Comparator:* "Women with vaginismus non-treated" Included placebo and control groups	• Success of intercourse

BTA = botulinum toxin type A; RCT = randomized controlled trial; SR = systematic review; VAS = visual analogue scale.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
Dessie 2019[13] **Switzerland** Botulinum type A provided by Allergen, Allergen not involved in trial	Double blinded, placebo controlled RCT	Patients ≥ 18 years, with persistent myofascial pelvic pain rated at a 6 or more on the VAS at least 50% of the time over 3 months. Patients had a tight pelvic floor and pain upon palpitation of a 6 or higher on the VAS (10 cm). *Excluded:* Pregnant patients, breastfeeding patients, or those with contraindication for BTA	*Intervention:* 200U BTA in 20mL saline bilaterally in reported pain areas *Comparator:* Saline injections All participants started pelvic floor physical therapy 4 weeks after the injection for a total of 8 weekly sessions	Change from baseline to 2 weeks following treatment in: participant-reported pain (VAS) PFDI Changes in pain on palpitation Quality of life Medication use Adverse events
Diomande 2019[14] **Switzerland** Botulinum type A provided by Allergen, Allergen not involved in trial	First 3 months: RCT, double blinded, placebo‑controlled After 3 months: Exploratory analysis, unblinded. This exploratory analysis was not relevant to the current report, but involved the following: A second 100U injection was given to all members of cohort continuing to have symptoms (regardless of study arm) After 6 months (3 months post injection #2), patients in Arm C (placebo) continuing to have symptoms received a third injection (second	Patients ≥ 18 years, with provoked vestibulodynia, normal vulvoscopy, no infections, no concurrent therapy for vulvodynia, cessation of corticoid creams ≥ 2 weeks before trial, using contraception *Excluded:* Pregnant patients, lactating patients, patients with vulvar dermatoses, myasthenia gravis or Lambert Eaton Syndrome, patients using antidepressants, neuroleptic medication or other drugs that may interact with BTA	*Intervention (RCT):* BTA (50U in 1mL saline – Arm A) injected with a 25-gauge syringe in the subcutaneous layers of the dorsal vestibulum (0.5 mL per side) *Comparator (RCT):* BTA (100U in 1mL saline – Arm B) Placebo (Arm C)	Pain: - Cotton swab-provoked pain measured on a VAS (10 cm) - von Frey filaments - Marinoff dyspareunia scale (0 to 3) Frequency of sexual intercourse Treatment success (i.e., ≥ 2-point improvement on cotton swab VAS, or reported symptom free) *Follow-up:* 3 months (RCT) 6 months (Exploratory analysis – not relevant to the current report)

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
	injection of 100U BTA) The patients who received two injections were collapsed into one study arm and followed for 6 additional months, with no comparator group.			
Yaraghi 2018[15] **Iran** Funding: Vice Chancellor for research of Tehran University of Medical Sciences	Parallel design RCT	Patients who were not pregnant between 20 and 40 years of age diagnosed with primary vaginismus Lamont grade III or IV *Excluded:* Contraindications to receiving botulinum, previous history of treatment with botulinum or physiotherapy, infection at the injection site, diseases involving nerves and muscles, vulvodynia, cutaneous problems at the vulva or perineum, anal fissure, urinary duct or rectum disorders, and coagulation disorders	*Intervention:* 500U botulinum diluted in 1.5 cc of saline - 150–400 units in levator ani muscles injected at three points in both sides using a 23-gauge needle *Comparator:* Physiotherapy (relaxation exercises, functional electrical stimulation, desensitization, and sensation focus for 12 weeks)	Successful intercourse Sexual Functioning (Female Sexual Function Index)

BTA = botulinum type A; PFDI = pelvic floor distress inventory; RCT = randomized controlled trial; U = unit; VAS = visual analogue scale.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[8]

Strengths	Limitations
Weinberger 2019[11]	
- Multiple databases used with keywords provided, grey literature searched - Outcomes eligible for inclusion provided and clear - Study selection done in triplicate - No list of excluded studies, but many studies were exclusions (502) so may have not been feasible; reasons for exclusion of papers was provided - No meta-analyses performed for relevant intervention, so no risk of inappropriate grouping of studies - Conflicts of interest reported	- Eligible interventions and comparators not clear (appeared to be everything [i.e. all treatments, all comparisons], but not specified) - FSD symptoms provided but no details on cause of symptoms (i.e., pain, but no details on what condition it was caused by) - Unclear how data extraction was performed - No sources of funding reported for included studies - Not all relevant information extracted from included studies - No risk of bias or quality appraisal performed - No published protocol - Search conducted as of Feb 2016, SR published in 2019, large delay between publication and search dates
Maseroli 2018[12]	
- Protocol registered on PROSPERO prior to publication - Begg-adjusted rank correlation test used to assess bias - Quality of studies assessed using Cochrane, GRADE, and Effective Public Health Practice Project tool - Comprehensive literature search completed, close to publication date of study (2018) - Selection and data extraction done in duplicate - No conflicts of interest - Many study details reported, including number of patients, age, onset of symptoms, type of vaginismus	- Combined studies with different interventions together into one meta-analysis, which may not have been appropriate (e.g., pharmacotherapies vs. behavioural interventions), included studies together with different comparators (i.e., all observational studies with no control group combined with controlled studies, “no treatment” comparators combined with “placebo”) - Heterogeneity of observational studies quantified and significant (I^2: 68.59, $P < 0.0001$) - Only included studies with outcome of completion of sexual intercourse which may not be indicative of quality of life or function. For example, in patients with vaginismus severe enough that pain occurs without sexual contact, completion of sexual intercourse may not be an outcome of relevance. - 50 studies included in qualitative assessment but 46 included in quantitative assessment with no reasoning as to why 4 were excluded. - Exclusion reasons given, but not very specific (e.g., “no treatment”) - Standard deviations or interquartile ranges not specified - No sources of funding reported for included studies

FSD = female sexual dysfunction; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; PROSPERO = International Prospective Register of Systematic Reviews; RCT = randomized controlled trial; SR = systematic review; vs. versus.

Table 5: Strengths and Limitations of Clinical Studies using Down's and Black Checklist[9]

Strengths	Limitations
Dessie 2019[13]	
- Aim of study clearly described - No loss to follow-up after randomization - Nurse not involved in study prepared syringes hidden from both patient and physician (double-blinding) - Validated pain and outcome scales used to assess pelvic floor pain and distress - Randomization performed using computer generated randomization - Allocation concealed in opaque envelopes - All muscle palpitations done with equal strength (enough to blanch a fingernail) so assessors were calibrated - Placebo and BTA injection procedure identical - Sample size calculated for sufficient power - Analysis was intention-to-treat (although no drop outs occurred) - Distribution of data specified (non-normal), so non-parametric tests and medians used	- No statistical comparison between groups for demographic information - Numbers for change in pelvic floor distress inventory do not appear to match between table and graphs (e.g., in the table the change from baseline at 12 weeks was greater than at 6 weeks, but in the graph the change at 12 weeks was less than at 6 weeks); it is unclear which is correct. - All participants received physiotherapy sessions 4 weeks after the injections, therefore the longer-term results of the injections alone (at 6 weeks and 12 weeks) are unclear. Additionally, the majority of patients in the trial had failed on physiotherapy (had a history of the treatment) but ~20-30% had never done it before. Physiotherapy is often a first line treatment, so with the addition of the physiotherapy intervention halfway through the follow-up, these individuals may have had improvements from the physiotherapy alone, and not from the BTA injections. - Not all patients in either group completed the scheduled physiotherapy, so the population became a mix of patients who had completed therapy, and others who had not. - Injection placed based on participant's reported pain area, so varied between patients - Only women with severe pain included, which may limit generalizability - The majority of participants has other pain disorders, and the medications/treatment for these disorders were not controlled for in the analysis - Some outcomes reported in the methods not reported on in the results, unsure if selective reporting of outcomes
Diomande 2019[14]	
- Aim of study clearly described - P-values adjusted for low sample sizes (i.e., Fisher's exact test and Bonferroni correction), appropriate tests used (e.g., paired tests for before and after) - Clear outcome assessments and clear intervention/procedure detailed - Randomization performed using computer generated randomization - Allocation was concealed by nurse for RCT portion of study, syringes were prepared by nurse and hidden from both patient and physician (double blinding) - Standardized and validated pain measurements used (VAS scale, Von Frey filaments, Marinoff dyspareunia scale) - Placebo controlled trial, all patients received an injection	- Unclear the number of patients with full follow-up data for the exploratory analysis (n = 12 in text, n = 10 in tables) - Unknown what was considered a "serious" adverse event - May not be representative of all patients with provoked vestibulodynia as many patients do not seek treatment. Patients recruited from a tertiary vulval clinic, who had undergone other treatments previously (for a median of 52 months), with one quarter of patients having primary vestibulodynia. Findings may not generalize to patients with less severe pain, patients seeing primary doctors, or with primary vestibulodynia. - Power calculation performed, but allocation created unequal groups (with arm B having a smaller number

Table 5: Strengths and Limitations of Clinical Studies using Down's and Black Checklist[9]

Strengths	Limitations
- No conflicts of interest	of participants than the power calculation required) so unknown if enough power to detect a significant difference between groups -
Yaraghi 2018[15]	
- Aim of study clearly described - Eligibility/inclusion of study participants clear - Only included participants with level III or IV vaginismus, which may limit external generalizability, but creates a more homogenous population of individuals with more severe vaginismus - Balanced block method used to randomize patients so sample size was equal between groups - Allocation concealed with envelopes - Randomization sequence/allocation performed by person not involved with study - Intervention and comparator clearly described - Unclear, but appears that power calculations performed (power 80% and significance level 5%) - Appropriate statistical tests used - Demographic information collected very thorough - Main findings clearly described with P-values and standard deviations - Intervention and control groups recruited from the same population	- Due to design of study, physicians/physiotherapists performing the interventions could not be blinded to treatment - Specific P-values for baseline demographics not provided for all characteristics (stated to be insignificant for all in text) - Loss to follow-up of 21.6% (either through moving away or through refusal to continue treatment), with slightly more participants dropping out of the control group - Baseline characteristics reported for participants in study after dropout. Characteristics of these participants lost-to-follow-up not reported, so unknown if any attrition bias occurred (e.g., whether the group of patients remaining in the study matched the initial population, making generalizability limited) - No intention-to-treat analysis (used inverse probability of censoring weighted log-rank test) - Stated that 58 women with grade III vaginismus enrolled as well as "4 others", but unclear who these 4 individuals were or their conditions (as they were not included in the analysis) - FSFI at baseline did not appear to have been compared statistically between groups (appeared to be in "figure 1" – *"Figure 1 shows the mean differences in each of the six sexual function domains for each treatment group." Page 5* – but figure 1 was the study flowchart and did not follow from the text) ○ Graphical representation of "mean scores for the FSFI" showed significantly higher scores in the physiotherapy group when compared to the BTA groups, but it was unclear what time point was represented - No placebo group examined - Participants gathered from a private university setting and results may not be generalizable to the general population. Additionally, most participants were of high educational level (academic levels).

BTA = botulinum toxin type A; FSFI = female sexual functioning index; U = units; VAS = visual analogue scale.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Weinberger 2019[11]	
Five studies were identified that used BTA to treat female sexual dysfunction **BTA vs. Other treatment** One study examined patients who had failed on conventional therapies who underwent BTA injections. These patients were compared with patients who underwent the "conventional therapy" alone. "Success" was successful penetrative intercourse. - N = 12 - Mean age: 23 years - Follow-up: 3 months - Comorbidities NR - Patients has refractory vaginismus according to the title of the included study ○ 12 women underwent conventional behavioural therapy; out of these women, 6 succeeded and 6 failed ○ The 6 women who failed underwent BTA injections, with 5 successes and 1 failure ○ BTA injections were only used in patients who were refractory to the conventional treatment **BTA vs. Placebo** One study examined patients undergoing BTA injections compared with placebo - N = 29 - Mean age: 29.53 years - Follow-up: 6 months - Comorbidities NR ○ Women receiving BTA (Botox) had a mean VAS decrease from 7.44 to 5.14, *P* < 0.001 ○ Women receiving placebo had a mean VAS decrease from 7.63 to 5.13, *P* < 0.001 ○ No comparative numerical results reported ▪ *"However, the Petersen et al study, a RCT examining onabotulinum toxin A injections into the musculus bulbospongiosus for provoked vestibulodynia, showed no impact on VAS, FSFI, and quality-of-life measures when compared with saline placebo." (p244)* Three included studies examined patients who underwent BTA injections with no comparator (not relevant for this report).	*"4 Cohort studies provide support for the use of transvaginal onabotulinum toxin A for dyspareunia. Between 50 and 300 U were injected into the levator ani or, in 1 study, ulbospongiosus muscle. Studies utilizing the 10-point VAS as a measure of dyspareunia reported a mean range of decrease between 2.3 and 4.47, notably greater than the MCID. However, the Petersen et al study, a RCT examining onabotulinum toxin A injections into the musculus bulbospongiosus for provoked vestibulodynia, showed no impact on VAS, FSFI, and quality-of-life measures when compared with saline placebo." (p244)* *"The cohort studies examining transvaginal onabotulinum toxin A for dyspareunia suggest that it is an effective treatment for dyspareunia secondary to vaginismus but not vestibulodynia. Provoked vestibulodynia involves pain with insertion of an object into the vagina or with applied pressure to the vestibule, and therefore is unlikely due to muscular spasm. Hence, it is not surprising that onabotulinum toxin A is less efficacious in this group." (p245-246)*

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Maseroli 2018[12]	
5 studies were identified regarding botulinum toxin injections - One study was also included in Weinberger 2019 (reported above),[11] with no additional details provided - Three studies did not include a control group (either placebo or other treatment, not relevant for this report) **BTA vs. Placebo** One study examined patients undergoing BTA 25U injections in bulbospongiosus muscle compared with placebo (saline) in primary vaginismus - N = 13, (BTA n = 8, placebo n = 5) - Mean age: 26.6 years - Follow-up: NR ○ Number of successes: BTA n = 8, placebo n = 0, *P* = NR ○ Global quality rating for this study was weak[a] **Meta-analysis** Event (successful intercourse) rate = 0.786 (95% confidence interval, 0.740 to 0.826), *P* = 0.000	*"We did not find any significant difference among the kinds of intervention (Q value [Q] = 1.74, P = 0.63); similar results were observed when only studies using botulinum local injections were considered among the ones on pharmacological therapy (success rate 0.78 [0.74 – 0.83]; Q = 1.65, P = 0.65)." (p1759)* *"The meta-analysis of observational studies indicates that women with vaginismus benefit from a range of treatments (behavioral sex therapy, CBT, pharmacological therapy, pelvic floor physiotherapy, and removal of hymenal remnants) in almost 80% of cases; no approach has proven superior to the others in allowing the achievement of penetrative intercourse." (p1762)*

BTA = botulinum toxin type A; CBT = cognitive behavioural therapy; CPP = chronic pelvic pain; FSFI = female sexual functioning index; NR = not reported; RCT = randomized controlled trial; U = unit; VAS = visual analogue scale.

[a] Global rating scale are ratings of strong, moderate, or weak (weak = lowest quality score).

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Dessie 2019[13]	
Demographics N = 59 BTA group n = 30 Placebo group n = 29 **Age, years, median [IQR]** BTA: 43 [30 to 55] Placebo: 40 [31 to 54] **BMI, median [IQR]** BTA: 23 [22 to 27] Placebo: 27 [24 to 29] **Nulliparous, number (%)** BTA: 11 (37) Placebo: 17 (59) **History of pelvic floor physical therapy, number (%)**	*"Onabotulinumtoxin A injections into the pelvic floor for myofascial pelvic pain were not more effective in decreasing muscle pain than saline injections. Adverse events from onabotulinumtoxin A were limited and similar to those from placebo." (p1.e2)* *"Onabotulinumtoxin A injection into the pelvic floor for patients with myofascial pelvic pain was not more effective at decreasing muscle pain 2 weeks after injection than saline in the most painful muscle group. Secondary outcomes, such as PFDI and Pelvic Pain and Urinary Urgency Frequency scores, demonstrated that onabotulinumtoxin A injection into the pelvic floor was not more beneficial than an injection of saline. Despite this, a higher percentage of participants who received onabotulinumtoxin A*

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
BTA: 23 (77) Placebo: 20 (69) **Sexually active, number (%)** BTA: 17 (57) Placebo: 8 (28) **Years of pain, median [IQR]** BTA: 7 [3 to 10] Placebo: 5 [3 to 10] **Other pain disorders, number (%)** BTA: 22 (73) Placebo: 23 (79) *"The intervention group had more participants rating their pain as severe or moderate at baseline compared with the placebo group." (p1.e4)* **BTA vs. Placebo, changes in pain from baseline, median (Wong-Baker FACES Pain Rating Scale)** **Left muscle group, BTA vs. placebo, median [IQR]** *Coccygeus* 2 weeks: –1 [–2 to –1] vs. –3 [–4 to –1], *P* = 0.046 4 weeks: –2 [–4 to –1] vs. –2 [–4 to –1], *P* = 0.72 12 weeks: –3 [–5 to –1] vs. –2 [–5 to –1], *P* = 0.390 *Iliococcygeus* 2 weeks: –2 [–3 to –1] vs. –2 [–5 to –1], *P* = 0.12 4 weeks: –1 [–3 to 0] vs. –1 [–4 to 0], *P* = 0.92 12 weeks: –3 [–5 to –1] vs. –2 [–4 to –1], *P* = 0.46 *Obturator onternus* 2 weeks: –1 [–3 to 0] vs. –1 [–5 to 0], *P* = 0.84 4 weeks:–2 [–4 to 0] vs. –2 [–4 to –1], *P* = 0.82 12 weeks:–3 [–5 to –3] vs. –3 [–3 to 0], *P* = 0.22 *Piriformus* 2 weeks: –1 [–3 to 0] vs. –2 [–4 to –1], *P* = 0.12 4 weeks: –2 [–3 to 0] vs. –2 [–4 to 0], *P* = 0.79 12 weeks: –2 [–4 to 0] vs. –2 [–6 to 0], *P* = 0.85 *Pubcoccygeus* 2 weeks: –1 [–3 to 0] vs. –1 [–5 to 0], *P* = 0.44 4 weeks: –1 [–3 to 1] vs. –2 [–4 to 0], *P* = 0.29 12 weeks: –3 [–6 to 0] vs. –3 [–5 to 2], *P* = 0.55 *Puborectalis* 2 weeks: –1 [–3 to 1] vs. 0 [–1 to 1], *P* = 0.39 4 weeks: –3 [–4 to –1] vs. –1 [–3 to 0], *P* = 0.31 12 weeks: –2 [–6 to –1] vs. –1 [–3 to 0], *P* = 0.21 **Right muscle group, BTA vs. placebo, median [IQR]**	*injection into the pelvic floor were more likely to report their overall pelvic pain as improved than those who received saline injections at 4 and 12 weeks after their injection, although this was statistically significant only at 4 weeks." (p1.e5-1.e6)*

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Coccygeus 2 weeks: –2 [–3 to 0] vs. –1 [–3 to 0], *P* = 0.50 4 weeks: –3 [–4 to –1] vs. –2 [–3 to 0], *P* = 0.19 12 weeks: –3 [–4 to 0] vs. –2 [–4 to 0], *P* = 0.54 *Iliococcygeus* 2 weeks: –1 [–3 to 0] vs. –1 [–3 to 0], *P* = 0.85 4 weeks: –1 [–5 to 0] vs. –3 [–4 to 0], *P* = 0.77 12 weeks: –3 [–5 to –1] vs. –1 [–3 to 0], *P* = 0.28 *Obturator onternus* 2 weeks: –1 [–3 to 0] vs. –1 [–4 to 0], *P* = 0.54 4 weeks: –2 [–3 to 0] vs. –2 [–4 to 0], *P* = 0.77 12 weeks: –3 [–6 to 0] vs. –2 [–5 to 1], *P* = 0.45 *Piriformus* 2 weeks: –2 [–3 to –1] vs. 0 [–3 to 1], *P* = 0.10 4 weeks: –2 [–4 to –1] vs. –1*P* = 0.0 [–3 to 0], *P* = 0.20 12 weeks: –3 [–4 to 0] vs. –1 [–4 to 0], *P* = 0.42 *Pubcoccygeus* 2 weeks: –1 [–3 to 1] vs. –2 [–3 to 0], *P* = 0.44 4 weeks: –2 [–3 to 0] vs. –1 [–4 to 0], *P* = 0.80 12 weeks: –3 [–5 to 0] vs. –1 [–3 to 2], *P* = 0.18 *Puborectalis* 2 weeks: –1 [–3 to 1] vs. 0 [–2 to 1], *P* = 0.37 4 weeks: –2 [–4 to 0] vs. –1 [–3 to 1], *P* = 0.54 12 weeks: –2 [–5 to –1] vs. –1 [–4 to 0], *P* = 0.22 **Change in pain from baseline, median [IQR] (VAS), BTA vs. placebo** 2 weeks: –0.3 [–3 to 1] vs. –0.3 [–2 to 0.1], *P* = 0.65 4 weeks: –1 [–4 to 0] vs. –0.2 [–1 to 0.8], *P* = 0.16 12 weeks: –1 [–4 to 0] vs. 0 [–4 to 1], *P* = 0.16 **PFDI-20 change from baseline, median [IQR], BTA vs. placebo** 2 weeks: 3 [–14 to 22] vs. –10 [–27 to –4], *P* = 0.01 4 weeks: –3 [–22 to 6] vs. –18 [–38 to –2], *P* = 0.19 12 weeks: –7 [–21 to 11] vs. –21 [–64 to –2], *P* = 0.11 **BTA vs. Placebo, median pain score (VAS)** Baseline: *P* = 0.07 2 weeks: *P* = 0.045* 4 weeks: *P* = 0.99 12 weeks: *P* = 0.94 *In favour of intervention (BTA) **BTA vs. Placebo, median PFDI[a] score** Baseline: *P* = 0.89 2 weeks: *P* = 0.12 4 weeks: *P* = 0.34 12 weeks: *P* = 0.23	

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
BTA vs. Placebo, median pelvic organ prolapse distress inventory score Baseline: *P* = 0.15 2 weeks: *P* = 0.06 4 weeks: *P* = 0.19 12 weeks: *P* = 0.18 **BTA vs. Placebo, median colorectal-anal distress inventory score** Baseline: *P* = 0.63 2 weeks: *P* = 0.19 4 weeks: *P* = 0.23 12 weeks: *P* = 0.81 **BTA vs. Placebo, median pain urgency frequency score** Baseline: *P* = 0.33 2 weeks: *P* = 0.22 4 weeks: *P* = 0.61 12 weeks: *P* = 0.23 **Patient Global Impression of Improvement index** 48.1% in intervention group rated severity as normal or mild at 12 weeks 63.0% in placebo group rated severity as normal or mild at 12 weeks *P* = 0.59 At 4 weeks, intervention group more likely to state improvement in symptoms (*P* = 0.03); at 12 weeks, intervention numerically more likely to state improvement in symptoms but this was not statistically significant (*P* = 0.10).	
Diomande 2019[14]	
Demographics N = 33 - BTA 50U n = 12 - BTA 100U n = 9 - Placebo n = 12 *Age, median [IQR]:* Full cohort: 27 [24 to 30] BTA 50U: 27 [25 to 28] BTA 100U: 28 [23 to 35] Placebo: 27 [23 to 30] *P* = 0.97 *Primary PVD, n (%):* Full cohort: 7 (22) BTA 50U: 3 (25) BTA 100U: 2 (25) Placebo: 2 (17) *P* = 0.99 *VAS during intercourse (0 to 10), median [IQR]:*	*"The randomized controlled trial showed no significant differences in pain levels when comparing treatment arms at 3 months. Hence, the efficacy of a single 50- or 100-units BT injection subcutaneously in the dorsal vestibulum compared to placebo could not be demonstrated. However, significant improvements in the von Frey filament measurements were detected within all groups at 3 months after all single injections. Likewise, findings from our supplemental exploratory analysis with repeat injections of 100 U BT over 6 months led to significant pain reduction. Between 41% and 58% of patients reported ≥ 2 VAS score reduction or no dyspareunia (symptom-free) after repeat injections of 100 U BT." (p998)*

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Full cohort: 8 [5 to 9] BTA 50U: 8 [7 to 9] BTA 100U: 8.5 [7 to 9] Placebo: 8 [8 to 9] *P* = 0.858 *Use of oral contraceptive, n (%):* Full cohort: 23(72) BTA 50U: 8 (67) BTA 100U:4 (50) Placebo: 11 (92) *P* = 0.14 No significant differences between groups in BMI, marriage status, nulliparity, smoking status, employment status, history of physical abuse, having friends with similar symptoms, intercourse within the last month, duration of PVD, duration of previous PVD treatment, bladder complaints, other pain syndromes, or prior vulvar surgery (all *P* > 0.05) All patients had undergone previous local therapy prior to trial **RCT (0 to 3 months follow-up):** ***Baseline:*** *Cotton swab provoked VAS (0 to 10), mean (SD):* BTA 50U: 6.6 (2.01) BTA 100U: 7.4 (1.85) Placebo: 7 (2.22) *P* = 0.735 *Von Frey Filaments[b] median [IQR]:* BTA 50U: 4.31 [4.25 to 4.61] BTA 100U: 4.17 [3.9 to 4.31] Placebo: 4.17 [3.84 to 4.74] *P* = 0.257 *Marinoff dyspareunia scale[c] (0 to 3), median [IQR]:* BTA 50U: 2 [2 to 3] BTA 100U: 2.5 [1 to 3] Placebo: 2 [2 to 3] *P* = 0.838 ***At 3 months follow-up:*** *Cotton swab provoked VAS (0 to 10), mean (SD):* BTA 50U: 6.2 (2.60) BTA 100U: 6 (1.77) Placebo: 6.5 (1.31) *P* = 0.857 *Von Frey Filaments,[a] median [IQR]:* BTA 50U: 4.74 [4.63 to 4.93] BTA 100U: 4.695 [4.14 to 5.18] Placebo: 4.56 [4.17 to 4.93]	

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
P = 0.616 *Marinoff dyspareunia scale (0 to 3), median [IQR]:* BTA 50U: 1.5 [0 to 2] BTA 100U: 1.5 [0 to 3] Placebo: 2 [1 to 2] *P* = 0.927 ***BTA 50U baseline vs. 3 months*** Cotton swab provoked VAS: *P* = 0.41 Von Frey Filaments: *P* = 0.028 Marinoff dyspareunia scale: *P* = 0.031 ***BTA100U baseline vs. 3 months*** Cotton swab provoked VAS: *P* = 0.239 Von Frey Filaments: *P* = 0.017 Marinoff dyspareunia scale: *P* = 0.276 ***Placebo baseline vs. 3 months*** Cotton swab provoked VAS: *P* = 0.623 Von Frey Filaments: *P* = 0.016 Marinoff dyspareunia scale: *P* = 0.102 **Safety and adverse events** No serious adverse events reported No episodes of urinary or stool incontinence Pain upon injection (88%) that resolved in 24 hours **Other Outcomes** No significant changes in frequency of intercourse between or within groups (*P* = NR) **Exploratory analysis (> 3 months follow-up):** N = 12 (n =10 in table), all patients received two consecutive injections of 100U BTA, 3 months apart *Cotton swab provoked VAS (0 to 10), mean (SD):* Baseline: 7.35 (2.06) 6 months follow-up: 5 (2.21) *P* = 0.029 *Von Frey Filaments[b] median [IQR]:* Baseline: 4.17 [3.84 to 4.56] 6 months follow-up: 4.93 [4.74 to 5.46] *P* = 0.003 *Marinoff dyspareunia scale (0 to 3), median [IQR]:* Baseline: 2 [2 to 3] 6 months follow-up: 1 [1 to 2] *P* = 0.059	

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Success rate (i.e., symptom-free or ≥ 2 VAS point improvement) across all patients 58%	
Yaraghi 2018[15]	
Demographics N = 58 BTA group n = 30 Control group n = 28 *Age, mean (SD)* BTA: 30.8 (3.9) Control: 28.8 (5.8) *P* > 0.05 Duration of vaginismus, mean (SD) **BTA: 5.11 (2.3)** **Control: 3.57 (2.11)** ***P* > 0.05** **Sexual trauma, n (%)** BTA: 2 (6.6) Control: 1 (3.6) *P* = NS Painful intercourse, n (%) BTA: 20 (66.7) Control: 19 (67.9) *P* = NS Not able to have intercourse, n (%) BTA: 10 (33.3) Control: 9 (32.1) *P* = NS Education level, n (%) Secondary - BTA: 2 (6.7) - Control: 5 (17.9) Diploma - BTA: 4 (13.3) - Control: 6 (21.4) Academic - BTA: 24 (80) - Control: 17 (60.7) *P* = 0.24 **BTA vs. Physiotherapy** *Time to response to treatment duration, months (SD)* - BTA: 6.7 (3.3) - Control: 8.3 (4.3) - *P* = 0.37	*"Evaluation of the efficacies of physiotherapy and botulinum toxin revealed that the standard method of physiotherapy with FES techniques and desensitization had a higher success rate than botulinum toxin injections in all sexual functioning domains and this difference was statistically significant. Also, evaluation of each group before and after treatment demonstrated that lubrication and desire failed to show a significant improvement in the intervention group. Nevertheless, the available evidence was not sufficient for vaginismus treatment based on the applied treatment processes in the selectively treated patients" (p5)*

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Within group differences *Sexual dysfunction, n (%), before treatment vs. after treatment* BTA: 28 (93.3) vs. 20 (66.7), *P* = 0.008 Control: 25 (89.3) vs. 11 (39.3), *P* < 0.001 Total population: 53 (91.4) vs. 31 (53.4), *P* < 0.001 **FSFI, mean difference in score (SD)** *BTA* Desire: 0.04 (0.79), *P* = 0.79 Arousal: 0.24 (0.36), *P* = 0.008 Lubrication: 0.02 (0.11), *P* = 0.96 Orgasm: 0.82 (1.4), *P* = 0.003 Satisfaction: 0.48 (0.6), *P* = 0.025 Pain: 1.57 (1.7), *P* < 0.001 *Control* Desire: 1.07 (1.39), *P* < 0.001 Arousal: 1.96 (2.36), *P* < 0.001 Lubrication: 2.41 (2.0), *P* < 0.001 Orgasm: 2.23 (1.94), *P* < 0.001 Satisfaction: 1.5 (1.1), *P* < 0.001 Pain: 3.18 (2.34), *P* < 0.001 **Between group differences** *Successful intercourse, n (%)* BTA: 20 (66.6) Control: 26 (92.9) *P* = 0.014 *FSFI, mean difference in scores, BTA vs. control* Desire: *P* = 0.001* Arousal: *P* < 0.001* Lubrication: *P* < 0.001* Orgasm: *P* = 0.001* Satisfaction: *P* = 0.001* Pain: *P* = 0.005* *All in favour of physiotherapy	

BMI = body mass index; BTA = botulinum toxin type A; FSFI = female sexual functioning index; IQR = interquartile range; NR = not reported; NS = not significant; PFDI = pelvis floor distress inventory; PVD = provoked vestibulodynia; RCT = randomized controlled trial; SD = standard deviation; U = units; VAS = visual analogue scale.

[a] PFDI-20 has 3 subscales: the Pelvic Organ Prolapse Distress Inventory; the Colorectal-Anal Distress Inventory; and the Urinary Distress Inventory-6.

[b] Von Frey filaments are 20 monofilaments with increasing log force value ranging from 1.65 to 6.65. Testing locations on the vulvar vestibulum were at 1, 3, 5, 6, 7, 9 and 11 o'clock.

[c] Marinoff dyspareunia scale: 0 = no problems, 1 = discomfort that does not affect completion (of intercourse), 2 = pain interrupts or prevents completion, 3 = pain prevents any attempts at intercourse.

Appendix 5: Overlap between Included Systematic Reviews

Table 7: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Weinberger 2019[11]	Maseroli 2018[12]
Bertolasi 2009	X	X
Fageeh 2011	X	X
Ghazizadeh & Nikzad 2004		X
Pacik & Geletta 2017		X
Ramzy 2015		X
Shafik & El-Sibai 2000		X
Morrissey 2015	X	
Pelletier 2016	X	
Petersen 2009	X	

Appendix 6: Additional References of Potential Interest

Previous CADTH reports

Ndegwa S, Cunningham J. Botulinum toxin A for the management of pelvic pain and urinary incontinence in women: a review of the clinical-effectiveness and safety. Ottawa (ON): CADTH; 2009 May:
https://www.cadth.ca/media/pdf/L0095_Botox_for_Pelvic_Pain_final.pdf

Ho C, Nkansah E. Botulinum Toxin A for muscle spasm of various anatomic origin: a review of the clinical effectiveness. Ottawa (ON): CADTH; 2008 Oct:
https://www.cadth.ca/sites/default/files/pdf/htis/Botulinum%20Toxin%20A%20for%20Muscle%20Spasm%20of%20Various%20Anatomic%20Origin%20A%20Review%20of%20the%20Clinical%20Effectivenes.pdf

Ho C, Nkansah E. Botulinum Toxin A for various pain syndromes: a review of the clinical effectiveness. Ottawa (ON): CADTH; 2008 Oct:
https://www.cadth.ca/sites/default/files/pdf/l0048_btxa_various_pain_syndromes_htis-2.pdf

Botulinum Toxin A for myofascial pain syndrome: a review of the clinical effectiveness. Ottawa (ON): CADTH; 2014 Sep:
https://www.cadth.ca/sites/default/files/pdf/htis/dec-2014/RC0591%20Botox%20for%20Myofascial%20Pain%20Final.pdf

Ho C, Nkansah E Botulinum Toxin A for myofascial pain syndromes: a review of the clinical effectiveness. Ottawa (ON): CADTH; 2008:
https://www.cadth.ca/sites/default/files/pdf/htis/Botulinum%20Toxin%20A%20for%20Myofascial%20Pain%20Syndromes%20A%20Review%20of%20the%20Clinical%20Effectiveness.pdf

Systematic Reviews – No Results Reported

Cheong YCS, G.; Willliams, A.C.de.C. Non-surgical interventions for the management of chronic pelvic pain. *Cochrane Database Syst Rev*. 2014.

Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes -an evidence based review. *Toxicon*. 2018;147:120-128.

Conference abstract

Meister M, Brubaker A, Sutcliffe S, et al. 75: Effectiveness of botulinum toxin injection to the pelvic floor for treatment of pelvic floor myofascial pain in women: a systematic review and meta-analysis. *AJOG*. 2019 Mar;220(3):S754.
https://www.ajog.org/article/S0002-9378(19)30133-4/fulltext
Accessed 2019 Aug 22

Review Article

Moga MA, Dimienescu OG, Balan A, Scarneciu I, Barabas B, Ples L. Therapeutic approaches of Botulinum Toxin in gynecology. *Toxins (Basel).* 2018;10(4):21.