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REVIEW ARTICLE

Methodological approaches to botulinum toxin for the treatment of chronic pelvic pain, vaginismus, and vulvar pain disorders

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Abstract

Introduction and hypothesis Botulinum toxin (BoNT) is increasingly used for pain, especially with muscle spasm. We describe our methodology for BoNT treatment of chronic pelvic pain (CPP) in women and place it in the context of the literature on techniques for this use.

Methods Databases were searched using terms "botulinum toxin," "pelvic pain," and "vaginismus." Reports on vaginismus/vulvodynia/vestibulodynia (included if pelvic floor muscles were injected) were grouped as "vaginismus/vulvar pain disorders" (*V*/VPD). We analyzed the type of report, condition, toxin serotype/brand, dose/dilution, muscle selection, guidance technique, and anesthesia. Publications from the same authors without unique information were combined for specific analyses.

Results Thirty-eight reports had analyzable information; many lacked complete information. Most were open-label prospective reports; there were four technical reports, one randomized comparison of doses and one placebo-controlled study of efficacy. Pelvic floor muscles were approached transvaginally, transperineally or transgluteally. BoNT brand/dose/dilution varied widely. Muscle localization techniques included anatomical landmarks only, electromyography, electrical stimulation with/without ultrasound, and fluoroscopy/CT scanning. Papers discussing analgesia utilized general anesthesia, conscious sedation with/without topical/local anesthesia, topical/local agent alone or pudendal block before or after injection. Cumulatively, 58–100% of patients with CPP and 71–100% of those with *V*/VPD improved. Serious adverse events (transient fecal incontinence/constipation, urinary incontinence/retention) were more frequent with higher doses.

Conclusions BoNT can be safely and tolerably injected into pelvic floor muscles in women as an out-patient procedure. This study identifies methodological factors to be considered in future studies and the critical need for high-quality clinical trials for this emerging treatment.

Keywords Botulinum toxin · Chemodenervation · Chronic pelvic pain · Pelvic floor spasm · Pelvic pain · Vaginismus

Introduction

Chronic pelvic pain (CPP) is an exceedingly common, potentially debilitating condition with a prevalence of 6–26% among women of reproductive age [1]. CPP, defined as "persistent pain in the lower abdomen or pelvis of a minimum 6-month duration that does not occur exclusively with menstruation, pregnancy or intercourse," is estimated to account for 20–40% of gynecological outpatient appointments and 3.8% of primary care visits [2, 3]. These estimates probably underestimate the impact, as only about one third of women with CPP seek medical attention.

Pelvic pain can arise from any pelvic structure including the reproductive organs, bladder, bowel, peritoneum, blood vessels, nerves, muscles, and bones. The possible causes are similarly diverse, including infection, inflammation, vasculopathy, neoplasm, endometriosis, and spasm. Chronic pelvic pain can arise without any identifiable etiology or anatomical lesion and can persist after treatment of any known precipitant. For example, endometriosis-associated CPP often cannot

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be explained solely by persistent endometriosis lesions or hormonal effects. In endometriosis, in addition to CPP of other causes, there is likely both peripheral and central sensitization that sustains chronic pain [4–6]. Peripherally, myofascial trigger points and spasm are present in pelvic floor muscles [4, 7]. Central sensitization, a mechanism that contributes to ongoing pain after resolution of the immediate pain trigger can manifest as lowered pain thresholds, allodynia, and hyperalgesia, and has been demonstrated for fibromyalgia, endometriosis, vulvodynia, and dysmenorrhea [4, 6, 8–11]. Central sensitization is associated with the release of pro-inflammatory molecules (e.g., substance P and calcitonin gene-related protein (CGRP) [12]).

One treatment for pain with possible effects on central sensitization is botulinum toxin (BoNT) [13, 14]. Although initially focused on neuromuscular pain, the use of BoNT now extends to many painful conditions, including those without overt muscle spasm, such as chronic migraine, neuralgias, and neuropathies, in addition to overactive bladder [15–17]. In muscle, BoNT blocks acetylcholine release from presynaptic neurons at the nicotinic neuromuscular junction. The mechanism in pain likely relates to its ability to similarly block the release of pain-associated pro-inflammatory neurochemicals, including glutamate, CGRP, and substance P. Thus, when applied to CPP, BoNT may not only target peripheral sources of pain such as pelvic floor muscle spasm, but may also reduce peripheral and central sensitization [14, 18].

Four brands of toxins are currently FDA-approved in the USA for various indications. OnabotulinumtoxinA (onaBoNTA: Botox; Allergan, Irvine, CA, USA), abobotulinumtoxinA (aboBoNTA: Dysport; Ipsen Pharmaceuticals, Basking Ridge, NJ, USA), and incobotulinumtoxinA (incoBoNTA: Xeomin; Merz Pharmaceuticals, Frankfurt, Germany) are serotype A toxins. RimabotulinumtoxinB (rimaBoNTB: Myobloc; Solstice Neurosciences, South San Francisco, CA, USA) is serotype B. BoNT dosing is based on "units," (1 Unit = LD50 for mouse intraperitoneal injection). Owing to differences in manufacturing, each brand is dosed differently.

The initial report of BoNT being used for a painful pelvic, nonbladder condition, in 1997, was the successful treatment of a single patient with vaginismus [19]. A series of uncontrolled, open-label studies examined onaBoNTA use for the treatment of levator ani spasm, showing a reduction in resting pelvic floor pressure and significant improvement in dyspareunia and nonmenstrual pelvic pain [20, 21]. A subsequent masked, randomized, placebo-controlled trial in 60 women with CPP showed improvement in pain in both active drug and placebo groups, with improvement in nonmenstrual pelvic pain only unique to the active drug group [22]. The authors suggested that needling alone may have accounted for acupuncture-like pain relief in both cohorts. Except for this controlled trial, the growing body of literature on the use of BoNT to treat vaginismus, vulvodynia, and CPP consists largely of case reports, case series, and uncontrolled trials. These reports are overwhelmingly positive.

For our practice, and for a clinical trial of BoNT in women with CPP, we developed our own approach to performing injections, drawing on over 25 years' experience with therapeutic BoNT (BK) and with the treatment of CPP (PS) [23]:

1. Pelvic examination is focused on the pelvic floor to identify areas of spasm and most intense elicited pain to select pubococcygeus, iliococcygeus, and obturator internus sites for injection.
2. Pre-medication with 5–10 mg diazepam is administered orally 20–30 min before the procedure.
3. Local anesthesia with 4–5% topical lidocaine/prilocaine cream/gel is applied to the vaginal mucosa over areas of spasm 20 min before the procedure.
4. The patient is placed in the dorsal lithotomy position.
5. External genitalia and vagina are cleaned with povidone/iodine. An alternative agent is used for those with iodine allergies.
6. Toxin is injected transvaginally into selected pelvic muscles targeting areas of maximal spasm. The sheathed needle is guided into position manually. The needle tip is advanced beyond the sheath and a few millimeters through the mucosa into muscle. The 4 cc volume of 100 U onabotulinumtoxinA is divided among 4–6 injection sites, following the pain and spasm, under EMG guidance using a 27-g, 3″ EMG electrode/injection needle.
7. The patient is observed in the clinic until cleared for discharge with an escort.

We chose onaBoNTA based on its long history as the first USA FDA-approved BoNT and favorable safety profile. We used a fixed dose of 100 units predicated on experience treating neurological disorders with excessive muscle contraction, such as spasticity and dystonia, and on convenience, as onaBoNTA is packaged in 100-U vials. We prepared the 100-U vial of toxin with 4 cc normal saline to provide enough volume to spread throughout the injected muscles while retaining the ability to deliver the entire dose within a limited number (4–6) of injection sites. We injected transvaginally, the most direct approach to the pelvic floor muscles. To minimize the risk of infection, we cleansed the vagina with a topical antimicrobial. We used EMG to ensure accurate placement of the needle in, and not through, the muscles. To enhance patient comfort, we used both an oral benzodiazepine and topical anesthetic on the vaginal mucosa. We avoided general anesthesia as relaxation of the pelvic floor muscles under anesthesia would prevent detection of spasm during the procedure. We piloted this technique in 7 women, randomized to either BoNT or saline placebo (data not published). We

found a trend toward longer pain relief in the BoNT cohort; however, interpretation of this small study was complicated as analysis revealed that those randomized to BoNT had lower pre-treatment pain severity than those assigned to placebo. However, the data were promising enough to proceed to a double-masked, placebo-controlled study (NCT01553201).

Despite the lack of high-quality data on efficacy, BoNT is increasingly offered for the treatment of female CPP by a wide range of practitioners. Published reports reveal a plethora of approaches to injection for this indication, with variation in all aspects of technique, including toxin brand/type, dose, dilution, and muscle selection, in addition to localization techniques used to confirm needle position in muscle and analgesia/anesthesia. This variability makes outcome data difficult to interpret.

A recent evidence-based review of BoNT for pain syndromes [17] found BoNT to be "possibly effective" for female CPP based on level C evidence, including that there was only a single placebo-controlled trial as noted above. Prior reviews of BoNT for pelvic pain in women have not addressed procedural differences, including the selection of drug, dose, approach, and needle guidance technique, factors that influence outcome. For this study, we reviewed the literature on BoNT injection of the pelvic floor in women for these methodological details that aid the interpretation of their reported outcomes and might inform the design of future clinical trials and clinical practice.

Materials and methods

PubMed, Embase, and Scopus databases were searched using the terms "botulinum toxin," "pelvic pain," and "vaginismus". Data were extracted on the type of report, condition treated, toxin serotype/brand, dose, dilution, muscle selection, muscle guidance technique, analgesia/anesthesia, and other methodological information. We recorded any reported benefit and adverse events. Data were extracted independently by two investigators; differences were reconciled into a single dataset.

Reports of BoNT treatment for CPP in men and for painful or overactive bladder in women were excluded. Abstracts were included if they were at least partly informative about the technique of injection. Publications from the same research group that did not provide unique information and described the same injection technique were combined for particular analyses (Table 1). We considered studies on myofascial pelvic pain, pelvic muscle overcontraction or hyperfunction, and pelvic floor myalgia as "CPP." We included reports of BoNT for vaginismus and vulvar pain disorders (*V*/VPD) including vestibulodynia/vulvodynia, only if pelvic floor muscles were injected, as BoNT offers a similar approach to the treatment of these pelvic pain conditions. We did not include papers on *V*/VPD if BoNT was injected solely into superficial perineal muscles.

Results

Thirty-eight publications had sufficient information to be included in the analysis; consolidation of reports from the same authors yielded 28 non-overlapping descriptions of technique (Table 1). The number of publications increased over the past 5 years (Fig. 1). Nineteen (50%) of the 38 reports were prospective, open trials (Fig. 2, Table 1). There were only one randomized, double-blind, placebo-controlled study of efficacy [22] and one randomized, double-blind comparison of two doses [39]. Four papers (11%) were technical reports. Twenty-two reports (58%) addressed pelvic pain; 12 (31%) were on focal pain (Fig. 3, Table 1). Cumulatively, these publications provide information on injections in approximately 1,300 patients, with two studies contributing half of the reported patients [27, 50].

Botulinum toxin: drug, dose, concentration

The most frequent toxin used was onaBoNTA (16 studies; 47%) (Fig. 4, Table 1). AboBoNTA was evaluated in 5 studies (15%), including one study whose authors stated that their patients opted for "Botox" treatment, but the vial size used (500 U) is only available for aboBoNTA [36]. IncoBoNTA or rimaBoNTB were utilized in one report each (3%). Five reports (15%) used "type A" toxin without specifying the brand. Although most of the unspecified type A reports likely used onaBoNT based on the stated vial size, dose, and year of the report, toxin type was considered "type A/NOS" (not otherwise specified) for this paper. Six reports (18%) provided no information on the serotype/brand of toxin injected. Combining overlapping reports yielded 16 reports that identified both the toxin serotype and brand.

Although onaBoNTA and incoBoNTA are dosed similarly, each brand of toxin should be considered as a unique drug with a different therapeutic range. Dosing was therefore evaluated separately for each brand. Doses varied widely within each brand (Figs. 5, 6). OnaBoNTA doses ranged from 10 to 300 U and aboBoNTA doses from 20-500 U. The single study using incoBoNTA provided individualized doses between 100 and 400 U, whereas that reporting rimaBoNTB used 2,500 U. The onaBoNTA doses for CPP tended to be higher than those for *V*/VPD (Fig. 5).

All type A toxins require reconstitution for use, enabling the concentration to be adjusted; rimaBoNTB is sold in a solution at a fixed concentration. Not all studies stated the dilution used. For unique reports, the dilution varied widely (Fig. 7). Of 5 publications with aboBoNTA, 1 used a dilution of 200 U/mL [28], 1 used 20 U/ml [35], and 2 used 333 U/mL

Table 1 Reports included

Reference	Type of report	Number of patients reported	Diagnosis	Botulinum toxin used	Reports from the same authors
Abbott et al. [22]	Randomized, placebo-controlled, masked	60	Chronic pelvic pain	OnabotulinumtoxinA	Jarvis et al. [20] Nesbitt-Hawes et al. [24, 25]
Adelowo et al. [26]	Retrospective	29	Chronic pelvic pain	OnabotulinumtoxinA	
Bautrant et al. [27] (abstract)	Retrospective	420	Chronic pelvic pain	IncobotulinumtoxinA	
Bertolasi et al. [28]	Prospective open	39	Vaginismus/vulvar pain disorder	AbobotulinumtoxinA	
Bhide et al. [29] (abstract)	Prospective open	13	Chronic pelvic pain	Type A, not otherwise specified	
Brin and Vapnek [19]	Single case report	1	Vaginismus/vulvar pain disorder	OnabotulinumtoxinA	
Brown et al. [30]	Prospective open	2	Vaginismus/vulvar pain disorder	Type A, not otherwise specified	
Brueseke and Lane [31]	Single case report	1	Chronic pelvic pain	Not stated	
Dykstra and Presthus [32]	Prospective open	12	Vaginismus/vulvar pain disorder	OnabotulinumtoxinA	
El-Khawand et al. [33] (abstract)	Prospective open	14	Chronic pelvic pain	Type A, not otherwise specified	Morrissey et al. [34]
Evans and Porter [35]	Technical report	None		AbobotulinumtoxinA/onabotulinumtoxinA	
Fageeh [36]	Prospective open	6	Vaginismus/vulvar pain disorder	AbobotulinumtoxinA*	
Gajraj [37]	Single case report	1	Chronic pelvic pain	Not stated	
Ghazizadeh and Nikzad [38]	Prospective open	24	Vaginismus/vulvar pain disorder	AbobotulinumtoxinA	Ghazizadeh et al. [39]
Ghazizadeh et al. [39]	Randomized dose comparison	42	Vaginismus/vulvar pain disorder	AbobotulinumtoxinA	Ghazizadeh et al. [38]
Goldstein et al. [40]	Technical report	None			
Greenleaf et al. [41] (abstract)	Prospective open	12	Chronic pelvic pain	Type A, not otherwise specified	
Halder et al. [42] (abstract)	Retrospective	50	Chronic pelvic pain	Not stated	Halder et al. [43]
Halder et al. [43]	Retrospective	50	Chronic pelvic pain	OnabotulinumtoxinA	Halder et al. [42]
Jarvis et al. [20]	Prospective open	12	Chronic pelvic pain	OnabotulinumtoxinA	Abbott et al. [22] Nesbitt-Hawes et al. [24] Nesbitt-Hawes et al. [25]
Kieger et al. [44] (abstract)	Technical report	None			Zavridis et al. [45] Moreland et al. [46]
Moldwin and Fariello [47]	Technical report	None			
Moreland et al. [46] (abstract)	Prospective open	57	Chronic pelvic pain	OnabotulinumtoxinA	Kieger et al. [44] Zavridis et al. [45]
Morrissey et al. [34]	Prospective open	21	Chronic pelvic pain	OnabotulinumtoxinA	El-Khawand et al. [33]
Nesbitt-Hawes et al. [24]	Prospective open	37	Chronic pelvic pain	OnabotulinumtoxinA	Jarvis et al. [20] Abbott et al. [22] Nesbitt-Hawes et al. [25]
Nesbitt-Hawes et al. [25]	Prospective open	31	Chronic pelvic pain	OnabotulinumtoxinA	Jarvis et al. [20] Abbott et al. [22] Nesbitt-Hawes et al. [24]
Orasanu et al. [48] (abstract)	Single case report	1	Chronic pelvic pain	RimabotulinumtoxinB	
Pacik et al. [49]	Retrospective	20	Vaginismus/vulvar pain disorder	OnabotulinumtoxinA	Pacik et al. [50] Pacik et al. [51]
Pacik et al. [51]	Prospective open	31	Vaginismus/vulvar pain disorder	OnabotulinumtoxinA	Pacik et al. [50] Pacik et al. [49]
Pacik et al. [50]	Prospective open	241	Vaginismus/vulvar pain disorder	OnabotulinumtoxinA	Pacik et al. [49] Pacik et al. [51]
Park and Paraiso [52]	Single case report	1	Chronic pelvic pain	Not stated	
Pope and Mahajan [53] (abstract)	Retrospective	2	Chronic pelvic pain	OnabotulinumtoxinA	

Table 1 (continued)

Reference	Type of report	Number of patients reported	Diagnosis	Botulinum toxin used	Reports from the same authors
Quirino et al. [54] (abstract)	Prospective open	27	Chronic pelvic pain	Type A, not otherwise specified	
Romito et al. [55]	Retrospective	2	Vaginismus/vulvar pain disorder	Abobotulinumtoxin A	
Stratton et al. [23] (abstract)	Prospective open	11	Chronic pelvic pain	Onabotulinumtoxin A	
Thomson et al. [21]	Single case report	1	Chronic pelvic pain	Onabotulinumtoxin A	
Yoon et al. [56]	Prospective open	7	Vaginismus/vulvar pain disorder	Not stated	
Zavridis et al. [45] (abstract)	Prospective open	57	Chronic pelvic pain	Not stated	Kieger et al. [44] Moreland et al. [46]

[a] Paper states patients received "Botox," but vial size/dose is consistent with aboBoNTA

[36, 38]. A single study used 250 U/ml in one cohort and 125 U/ml in another cohort (Fig. 7) [39]. In the 10 reports on onaBoNT with dilution information, concentrations ranged from 3.6–100 U/mL [20–23, 26, 32, 35, 43, 50, 53]. One of these studies, comparing three different dilutions (10 U/ml, 20 U/ml, and 100 U/ml) of 40 U onaBoNTA for CPP, found no effect of dilution on efficacy [20]. The single report on incoBoNTA did not provide dilution information [27].

Prescribing information for type A toxins specifies reconstitution with preservative-free saline. Local anesthetics were sometimes used as the diluent to provide pain relief during and briefly after injection. Twelve non-overlapping publications on type A toxins reported the diluent. Nine studies used saline alone [23, 24, 31, 32, 36, 38, 39, 43, 56], 1 each used ropivacaine [35] or bupivacaine [37], and 1 used saline with bupivacaine [53].

Procedures

Muscles injected to treat CPP or *V*/VPD included some combination of obturator internus, levator ani (pubococcygeus, iliococcygeus, and puborectalis), or coccygeus. For V/VPD, bulbospongiosus and ischiocavernosus were sometimes included. Some practitioners injected a set combination of muscles with fixed injection sites within each muscle. Others used a "follow-the-spasm" approach, basing the muscle and sites within the muscles on examination and patient report.

In all the studies on V/VPD that were included, the transvaginal approach was used [19, 30, 32, 38, 39, 49, 50, 56, 57]. Of 11 reports on CPP with sufficient information, transvaginal injections were performed in 8 [20–24, 26, 31, 52] and transperineal injections were performed in 2 [24, 34]. In one, a transgluteal approach to the obturator internus was used [37].

Different localization techniques were used to guide needle placement or to confirm needle position in muscle. In 8 publications there was no information on needle localization technique [29, 36, 38, 41, 48, 52–54]. In 10 unique studies anatomical landmarks/manual palpation only were used [21, 22, 26, 31, 32, 40, 42, 47, 50, 56]. Electromyography (EMG) was employed in 6 studies [19, 23, 28, 30, 33, 55]. Electrical stimulation was used with or without ultrasound in 2 reports [27, 35]; 1 of which used 4D ultrasound [35]. In 2 studies fluoroscopy and/or CT scanning were used [37, 44].

Analgesia and sedation are important considerations for patient comfort during pelvic floor injections. In 11 unique papers there was no mention of anesthesia/sedation [19, 27, 28, 31, 40, 41, 44, 47, 48, 55, 56] and in 2 studies, the authors stated explicitly that no anesthesia was used [32, 52]. In 4 unique papers general anesthesia was reportedly used [25, 29, 35, 42]. In 7 conscious sedation was used alone [21, 26, 38] or with a topical or local anesthetic [20, 23, 36, 37]. In 1 a topical agent was used alone [30]; in another local

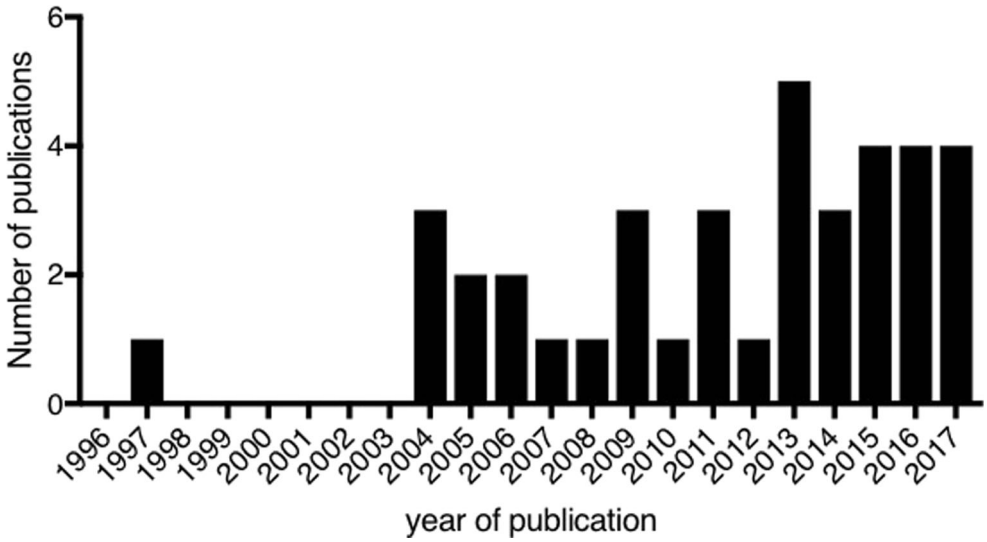

Fig. 1 Publications on pelvic floor botulinum toxin for female chronic pelvic pain and vaginismus/vulvar pain disorders

intramuscular anesthesia was used before injection and the procedure was followed by a pudendal nerve block [34]. One group placed a pudendal nerve block before toxin injection [36]. In 2 groups, BoNT injection was followed by bupivacaine injection to the same muscles [42, 50].

Adjunctive procedures were occasionally described. Two studies reported performing pelvic muscle massage immediately after injection [40, 43]. One of those groups also instructed patients to perform repetitive pelvic floor muscle contraction [40]. For *V*/VPD, one practitioner inserted lidocaine-coated vaginal dilators following injection while patients were still under anesthesia [58].

The most common primary outcome measure was patient self-report, usually based on a visual analog scale (VAS). The cumulative results are difficult to interpret as the type of data collected and presentation of results varied widely. Overall, excluding single case reports and duplicate reports, the response rates for CPP ranged from 58 to 100% among approximately 1,046 participants. In papers utilizing VAS to assess pain, scores decreased 19–100% [20, 22, 23, 26, 29, 30, 32, 34, 43, 54–56]. There were otherwise insufficient data to evaluate response by toxin brand, dose, or approach to injection.

The sole double-masked, placebo-controlled study of BoNT for CPP randomized 60 women with CPP and elevated pelvic floor pressure on vaginal manometry to onaBoNTA or placebo [22]. Eighty units of BoNTA at a concentration of 20 U/mL was injected under conscious sedation into two sites bilaterally, the puborectalis and pubococcygeus. Pain decreased in both the active drug and the placebo groups in all pain modalities, without statistically significant intergroup differences. There was, however, a significant decrease in resting pelvic floor pressure and a decrease in nonmenstrual pelvic pain compared with baseline in the BoNT cohort only.

In the 10 unique reports on *V*/VPD with more than one participant, 71–100% of 367 patients achieved intercourse or

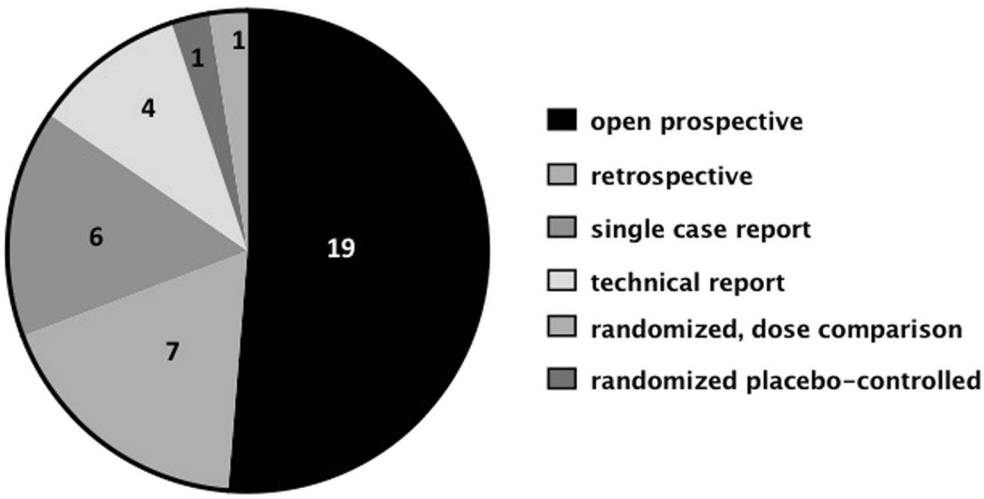

Fig. 2 Type of report on pelvic floor botulinum toxin for female chronic pelvic pain and vaginismus/vulvar pain disorders

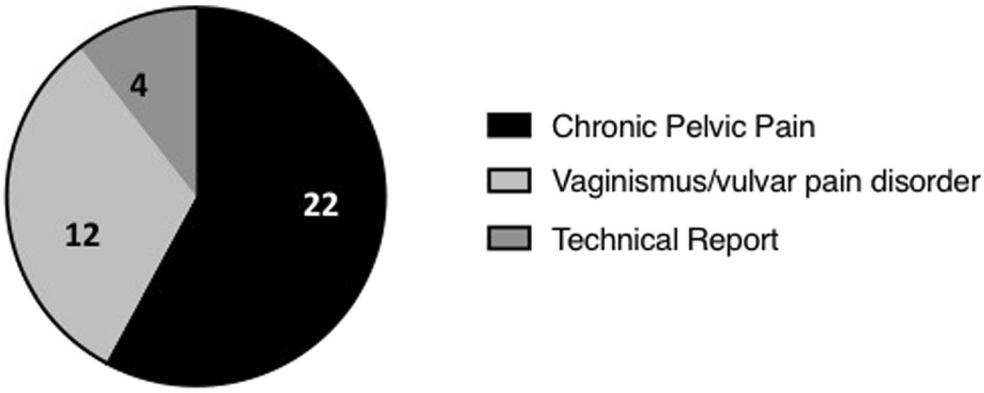

Fig. 3 Diagnosis studied for pelvic floor botulinum toxin

reported a significant decrease in pain with intercourse [19, 28, 30, 32, 36, 38, 39, 50, 55, 56]. Some patients with *V*/VPD had permanent resolution with a single injection session, whereas others required more than one session to achieve relief [19, 28, 30, 32, 36, 38, 55, 56].

Twenty reports, combining duplicates from the same authors, provided information on adverse events; 9 of whom identified no adverse effects [32, 36, 37, 45, 48, 53, 55, 56, 59]. Three studies reported adverse events attributable to the mechanics of injection, including injection site tenderness and minor bleeding [22, 30, 38]. The most frequent adverse effect likely due to BoNT itself was new or worsening urinary incontinence, usually stress incontinence [22, 26–28, 34, 50]. Urinary retention was also reported [26, 43] in addition to both constipation [26, 34, 39, 43] and new or worsening fecal incontinence [22, 26, 27, 34]. One report, using onabotulinumtoxinA doses of 100–300 U, found drug-related fecal incontinence and urinary retention mainly in those who received 300 U [26]. There was an adequate number of studies on onaBoNTA to determine that new fecal incontinence or constipation and new urinary incontinence or retention were associated predominantly with doses over 100 U (Fig. 8). Other adverse effects included flu-like symptoms [22], excessive vaginal dryness [50], and worsened vaginal prolapse [27, 34]. Drug-related adverse events were transient and similar with transvaginal and transperineal approaches. It was not otherwise possible to associate drug-related adverse events with a particular drug or technique. There was a single report of ischiorectal fossa abscess after transvaginal injection into the obturator internus and pubococcygeus for CPP [31].

Discussion

This review of the literature supports the use of BoNT for the treatment of CPP and *V*/VPD in women and provides an insight into how to use it. First, BoNT can be safely and

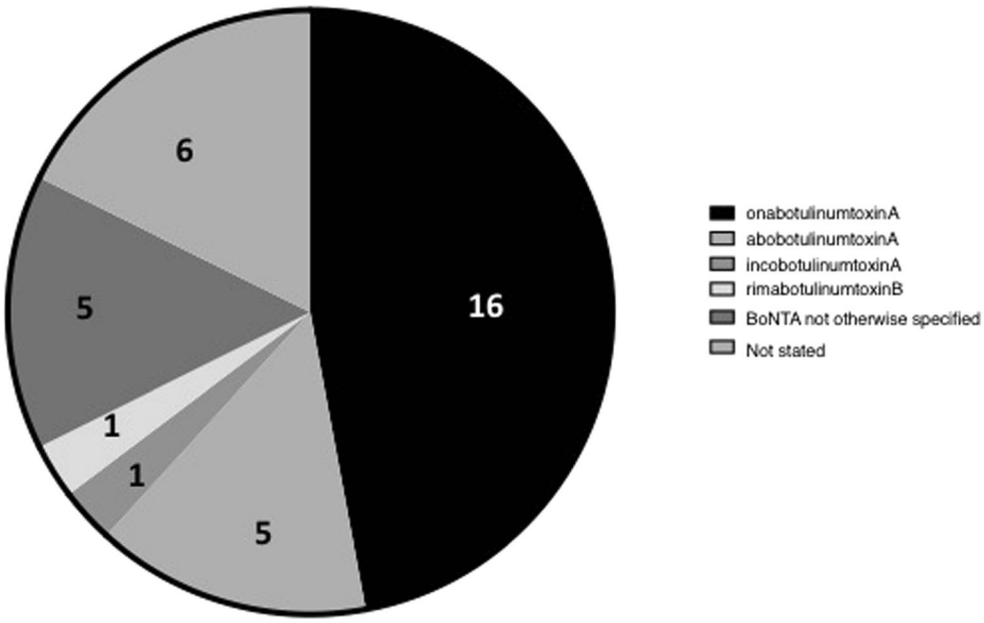

Fig. 4 Type/brand of toxin used for pelvic floor botulinum toxin

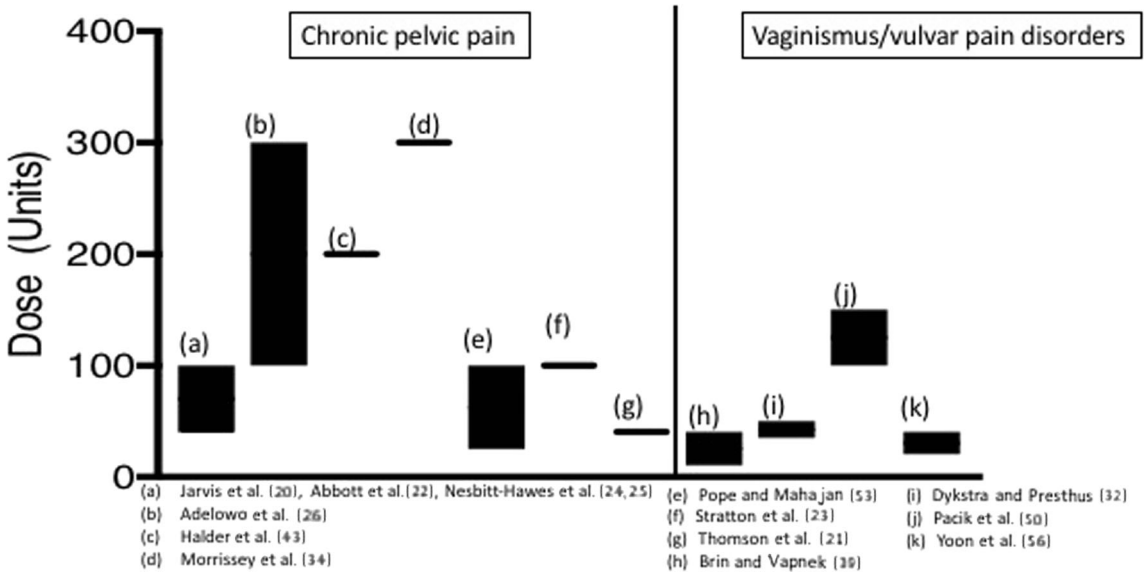

Fig. 5 OnabotulinumtoxinA dose for pelvic floor botulinum toxin. Each bar shows the dose range for a single report

tolerably injected into muscles of the pelvic floor and this treatment can be administered in the office or outpatient setting. Second, injections can be safely and tolerably given under conscious sedation. Tolerability may be enhanced by adding a topical or local anesthetic. General anesthesia is often not necessary. Practitioners should be aware that if general anesthesia is used, the sites of injection must be chosen in advance, as relaxation of the pelvic muscles under anesthesia makes it impossible to detect spasm during injection. Further study may delineate circumstances or patients for whom performing the procedure in the operating room is warranted. Although the manufacturers recommend mixing type A toxins in saline, some practitioners use anesthetics, such as bupivacaine, as the diluent to take advantage of the immediate antinociceptive effect. Caution is required with this approach, however, as the first reported case of anaphylaxis with BoNT injection occurred when the toxin was prepared in lidocaine [60].

For most other indications, BoNT types and brands are similar in efficacy, duration, and safety profile. For women with CPP or *V*/VPD, successful response was obtained with onaBoNTA doses ranging from 40 to 300 U for CPP and from 10 to 155 U for *V*/VPD. The single report with aboBoNTA for CPP used 300 U; for *V*/VPD, the aboBoNTA dose ranged from 40 to 500 U. The lack of correlation between dose and benefit is not surprising, as there is no direct correlation between dose and beneficial response when BoNT is used to treat dystonia, spasticity or other pain disorders. Also similar to BoNT use for other indications, evidence from this literature suggests that higher doses are associated with an increased risk for toxin-related adverse events.

Both retention and incontinence of urine or feces were reported as toxin-related side effects. These opposing symptoms may result from the variation in injection technique. The bowel and bladder adverse effects that emerge may depend on whether toxin spread from the site of injection is to the muscles used to expel urine or feces or the respective sphincters. The spread of toxin is, in turn, influenced by the muscle injected, needle placement, volume of injectate, and concentration and dose of toxin.

The most serious adverse event reported was an ischiorectal fossa abscess, attributed by the authors to the tracking of vaginal flora into the ischiorectal space [31]. The authors of this case noted that neither they nor other injectors reported using antiseptic preparation of the vagina before injection. Alternatively, without a guidance technique to ensure correct needle placement in the selected pelvic floor muscle

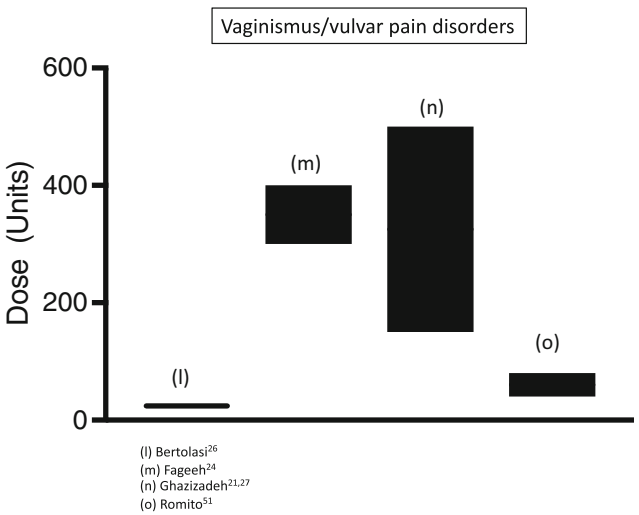

Fig. 6 AbobotulinumtoxinA dose for pelvic floor botulinum toxin. Each bar shows the dose range for a single report

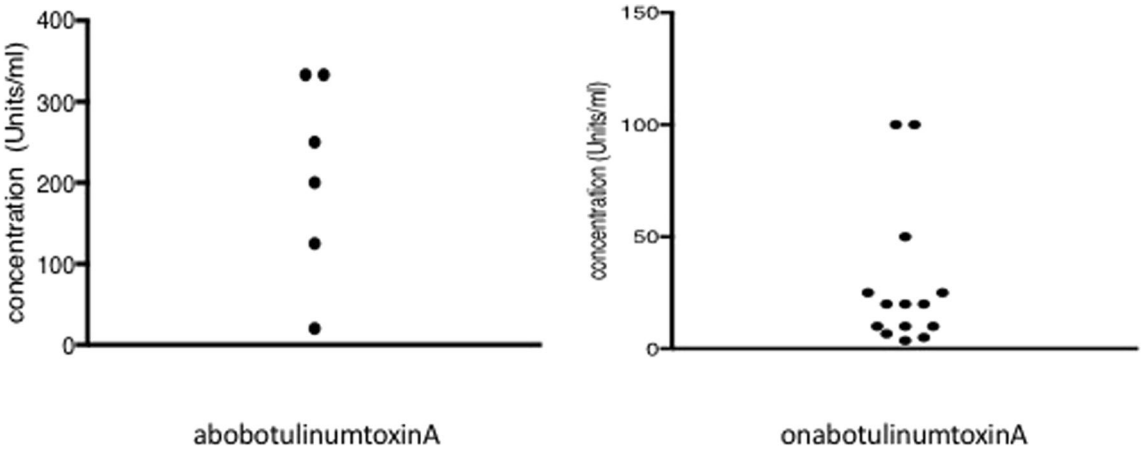

Fig. 7 Dilution of abobotulinumtoxinA and onabotulinumtoxinA for pelvic floor botulinum toxin. Each point represents a separate study or cohort within a study

and without consideration of the anatomical relationships pertaining to the bowel, bladder, and urethra, the needle may have traversed the rectal mucosa, tracking gastrointestinal flora into the ischiorectal fossa.

Regarding guidance techniques in the reports reviewed, EMG, electrical stimulation, and ultrasound can easily be used in the office setting. Fluoroscopy and CT would entail additional facilities and equipment, in addition to exposure to ionizing radiation.

The main limitation of this study is that of the literature itself—the low quality and lack of consistency and completeness in the information regarding key aspects of pelvic floor BoNT injection in women. Poor study quality, a paucity of randomized controlled trials and incomplete information on injection methodology, especially toxin brand/type and dose, preclude recommendations for a single optimal technical approach. Caution is also needed in interpreting the literature, as the high response rates across the studies may reflect reporting bias, a failure to publish negative outcomes, and, as suggested by the single masked, placebo-controlled trial, confounding by a high placebo response rate, as seen in many controlled studies on other types of pain.

Summary and conclusions

Our study supports the safety and tolerability of BoNT injection into the muscles of the pelvic floor in women. Although the lack of complete and essential information in published reports does not allow for recommendations for a single best

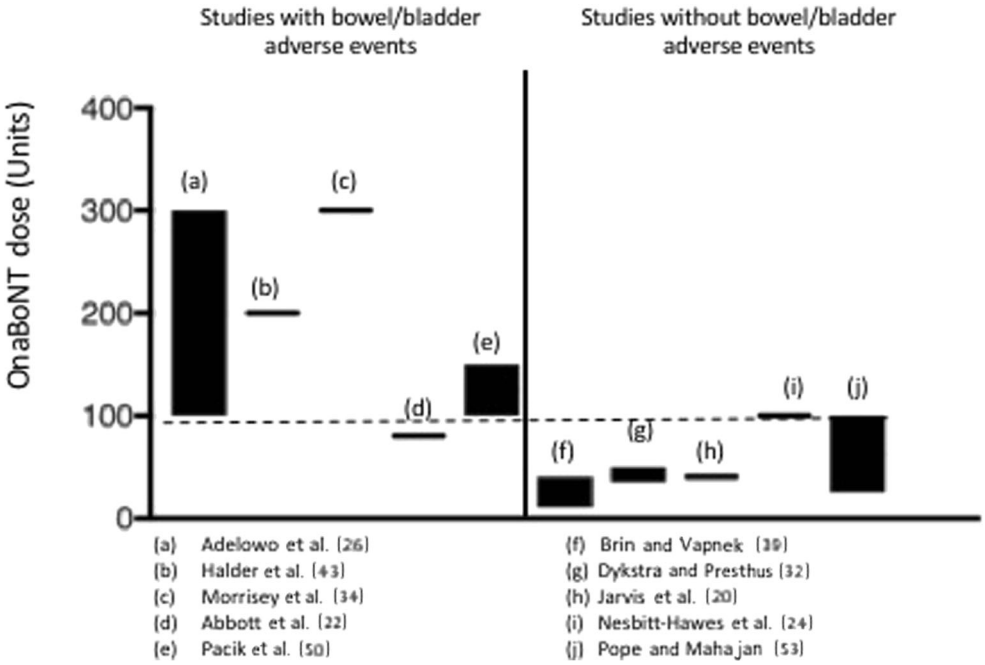

Fig. 8 Bowel or bladder adverse events in pelvic floor botulinum toxin studies by onabotulinumtoxinA dose

practice methodology, the reports illustrate that lower doses were associated with fewer bowel and bladder adverse effects, the importance of a needle guidance technique in addition to use of anatomical landmarks, and the tolerability of injection in the office setting. The currently published reports routinely omitted information critical to assessment of the technical approach, efficacy, and side effects, such as data on the type/brand of toxin and doses used, muscle selection, guidance techniques used for accurate needle placement, and outcome data. Researchers and clinicians will benefit from inclusion of these data in future publications.

We also highlight the striking absence of "gold-standard," randomized, double-masked, placebo-controlled trials, which are key to establishing the efficacy and safety of a treatment that is becoming increasingly widespread. Having reliable methodological data enables BoNT pelvic muscle injection procedures to be evidence-driven rather than based on individual provider preference. Properly designed and executed clinical trials and publications with complete methodological information are crucial.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest related to this article.

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