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Botulinum Toxin Treatment of Pelvic Floor Disorders and Genital Pain in Women

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ABSTRACT

Background and Objective
Botulinum neurotoxin (BoNT), now commonly used for reducing muscular spasms in other neuromuscular disorders, is now increasingly proposed also for treating pelvic floor disorders, including chronic pelvic pain syndromes, vaginismus, vulvodynia and vulvar vestibulitis syndrome. To provide up-to-date information on these advances we reviewed the literature about Bunt injections for pain and spasms related to pelvic floor disorders.

Methods
We conducted a Medline search using the terms botulinum neurotoxin, pelvic floor disorders, levator ani myalgia, vaginismus, vulvar vestibulitis , vulvodynia, dyspareunia, interstitial cystitis, recurrent cystitis, and postcoital cystitis. We sought information on the indications and techniques used for Bunt treatment for pelvic floor dysfunctions, and related pain syndromes in women.

Results
Our search identified 12 studies for review (including a randomized controlled trial) showing that Bunt effectively reduces pain in chronic genital pain syndromes associated with pelvic floor spasm. Before Bunt trials, patients with idiopathic lifelong vaginismus and dyspareunia, associated with hyperactive pelvic floor muscles, had no effective treatment options. Bunt injected under electromyographic (EMG) guidance in pelvic floor muscles improves vaginismus, helping to restore a normal sexual life. Bunt injections also seem to improve vulvodynia and vulvar vestibulitis. Though some patients need periodic injections, in about 65% of affected women BoNT achieves permanent benefit.

Conclusions
These encouraging evidence-based results suggest that BoNT injected intramuscularly should extend treatment options for women with lifelong or acquired pelvic floor disorders and genital pain.

INTRODUCTION

Pelvic floor disorders in women include widely ranging complaints such as chronic pelvic pain, lifelong vaginismus (LLV), vulvodynia, and vulvar vestibulitis syndrome (VVS) [1-5].

Chronic pelvic pain is reported to affect approximately 15% of women aged from 18 to 50 years [6]. Chronic pelvic pain refers to any pain in the pelvic region that lasts six months or longer. Pain is located over the entire area rather than limited to one spot. Chronic pelvic pain can be a symptom of another disease, or classified as a condition in its own right. Among the signs and symptoms are severe, steady pain, pain that comes and goes (intermittent), dull aching pain, sharp pains or cramping, and pressure or heaviness deep within the pelvis. The pain can be non menstrual, dysmenorrheic, dyspareunic, or occur during bowel movement (dyschesia). Spasms or tension of the pelvic floor muscles can lead to recurring pelvic pain. Chronic pain can originate from gynecologic problems including endometriosis, chronic pelvic inflammatory disease, pelvic congestion syndrome, ovarian remnant and fibroids. Other diseases that can cause pelvic pain include irritable bowel syndrome and interstitial cystitis. Pelvic pain may be exacerbated by psychological factors (depression or sexual abuse) [5]. In the diagnostic and therapeutic approach to chronic pelvic pain, the initial history and physical examination can narrow the diagnostic possibilities, guide any subsequent evaluation, and rule out malignancy or major systemic disease [7]. If the initial diagnostic work-up fails to disclose a specific cause, a limited laboratory and ultrasound evaluation will usually clarify the diagnosis, as well as rule out serious disease and

reassure the patient. Few treatment modalities have proved to benefit the symptoms of chronic pelvic pain. The currently preferred treatments are oral medroxyprogesterone, goserelin, and adhesiolysis for severe adhesions, and a multidisciplinary treatment approach for patients without a specific diagnosis [8,9]. The therapeutic effectiveness of oral analgesics, combined oral contraceptive pills, gonadotropin-releasing hormone agonists, intramuscular medroxyprogesterone, trigger point, neuromodulation, and hysterectomy remains less clear [5]. Many patients with chronic pelvic pain therefore still find effective treatment difficult to obtain hence their quality of life declines [5].

Vaginismus is defined as a painful spasm of unknown origin involving the pelvic floor muscles around the vagina thus precluding coitus, associated with a variable degree of phobia towards intercourse or any type of vaginal penetration (including fingers or other means) [10]. Vaginismus has a prevalence of about 1% and is often associated with bowel and bladder voiding difficulty [4]. Vaginismus is classified as primary idiopathic LLV or secondary (acquired) vaginismus when it appears months or years after the first intercourse and follows other diseases such as local inflammation. According to the Lamont classification vaginal and surrounding spasms are classified into four degrees of intensity (I to IV) [11]. Sometimes a phobia of sexual intercourse can be difficult to distinguish from vaginismus of the dystonic type [12] although patients history and behavior, gynecological examination and neurophysiological investigations [13] aid clinicians in distinguishing the psychogenic form from the dystonic type of vaginismus. In dystonic vaginismus LA investigation with EMG shows hyperactivity at rest and paradoxical activity during straining [13-15] and hyperexcitability of the late oligosynaptic response of the bulbocavernosus reflex [13]. Vaginismus interferes with sexual life: in the most severe cases it makes intercourse impossible and is the leading female cause of unconsummated marriages /relationships. In the least severe cases, it contributes to lifelong dyspareunia [4]. Vaginismus dramatically affects the social and familiar relationships. Treatment outcomes vary according to the severity of the phobic attitude and of the LA spasm. Lifelong vaginismus is currently managed with a multimodal approach including psychosexual therapy (with sexual education and behavioural therapy, aiming at increasing voluntary control of the pelvic floor muscles and accepting progressive vaginal dilatation), medications (antimycotics, anxiolytic drugs, antiphobic antidepressants and GABAergic inhibitors), biophysical therapy (local electromyographic biofeedback) and surgical interventions such as hymenotomy [16-18]. None of these treatments help the subset of patients with severe LA hyperactivity, or a severe phobic attitude.

Vulvodynia is characterized by vulvar pain, described as burning or stinging, or a feeling of rawness or irritation. Vulvodynia has a prevalence of about 15 % in the general population [20]. The pain can have an acute onset and in most cases becomes chronic lasting months to years. The local and generalized decrease in the tactile and pressure pain thresholds in patients with vulvodynia suggests a central sensitization component as happens in allodynia [21,22]. Vulvodynia may have multiple causes, including cyclic vulvovaginitis, vulvar vestibulitis syndrome (VVS), essential vulvodynia and vulvar dermatoses [1,23]. Current treatment of vulvodynia includes antidepressants, fluconazole, calcium citrate, anticonvulsants, biofeedback, pelvic floor physical therapy and surgery [2, 4,24,25].

VVS is an idiopathic disease consisting of vulvar erythema and often inducing pain during intercourse (superficial vaginismus) and also vaginal spasms (vaginismus according to the Lamont classification) [11, 26].VVS is currently considered a subset of vulvodynia [1,27]. The disease may have multifactorial causes including biological, psychosexual and relational factors [28]. As a multisystemic disease, it involves the mucous structure of the vulvar vestibule and the immune, muscular, vascular, and nervous systems, including pain fibers and centers [29,30]. Among the pathophysiologic factors most frequently held responsible for linking chronic inflammation and chronic pain is chronic inflammation, characterized by upregulation of mast cells and pain fibers [31]. Although infections or specific factors [1] may sometimes provoke VVS allowing successful treatment, VVS usually remains idiopathic. Tailored treatment may include oral drugs (antimycotic agents, myorelaxants, antidepressants and pain modulators such as amitriptyline, GABAergic inhibitors), local anesthetic nerve blockade [3,4,32,33], and surgical treatments including vestibulectomy [34,35].. Although treatment outcomes are satisfactory from 3 to 75 % of patients, some patients complain of persistent symptoms. Although many of these pelvic syndromes cause pain or distress, despite the various medical and surgical options proposed over the years many patients remain ineffectively treated, or, at best, report only minor improvement [4].

An alternative or adjunctive apparently successful approach for treating women suffering from pelvic floor disorders and genital pain, first introduced in the 1980s [36] and now attracting growing interest, is botulinum neurotoxin (BoNT). BoNT has already been reported to improve pain in various body parts such as neck [37], head [38,39] and low back [38,39]. Ample reviews have already addressed the various conditions currently managed with BoNT injections, for example movement disorders, spasticity, autonomic disorders including hyperhidrosis, and gastrointestinal tract dysfunctions [39-42].

BoNT is a polypeptide that inhibits binding of intracellular acetylcholine vesicles to the cell membrane at presynaptic level. BoNT injected into the affected muscles decreases muscle spasms and pain through various action mechanisms [38,43]. First, BoNT reduces muscular activity by inducing a presynaptic block of cholinergic synapses followed by muscular chemodenervation. Second, BoNT inhibits gamma motor endings in muscle spindles thus reducing Ia/II afferent signals and muscle tone without affecting muscle strength (reflex inhibition). Third, BoNT-A injected into muscles induces direct local analgesic effects probably by blocking release of the neurotransmitter substance P, glutamate and calcitonin gene-related peptide [43-45]. Although the central or peripheral mechanisms, or both,

underlying BoNT's actions in reducing muscle spasms and pain have been fully discussed [43] they remain controversial. In reducing pelvic floor spasms all these mechanisms probably act in concert [43]. BoNT therapy for patients with pelvic floor disorders and genital pain seems to have several advantages over previous treatments. The technique is simple, easy, costeffective, not time-consuming and can be done on an outpatient basis. Most patients tolerate BoNT injections well, and adverse effects are rare and transient [43]. A disadvantage is that re-injections are needed to maintain consistent benefits. The accumulating evidence showing the effectiveness of BoNT in treating pelvic floor disorders and genital pain makes this an appropriate moment to review these advances and identify new directions for future research.

Our aim in this review was to analyze and discuss current clinical evidence on the use of BoNT-A in treating pelvic floor disorders and genital pain in women. In doing so we hope to give clinicians caring for patients with pelvic disorders a balanced view of the current treatment options in
these disorders.

METHODS

We searched Medline and COCHRANE library data bases from 1985 to 2008 to identify all articles and reviews addressing the topic of BoNT-A use in pelvic floor disorders and genital pain. A further manual research was conducted on papers mentioned in the references of articles and not found with the previous Medline and Cochrane search techniques. We included case reports and when accessible controlled trials. We included only articles written in English. The following search terms were used: botulinum toxin, chronic cystitis, dyspareunia , female chronic pain syndromes, genital pain syndromes, recurrent cystitis, interstitial cystitis, vaginismus, vulvodynia, vestibulodynia and vulvar vestibulitis syndrome. We included published and unpublished data from our own studies.

RESULTS

We identified 12 studies that fulfilled our search criteria dealing with chronic pelvic pain, vaginismus, and vulvodynia. Our Medline search found no published studies on VVS. Of the 12 articles identified, 4 referred to BoNT injections for chronic pelvic pain syndromes [46-49], 4 to BoNT injections for vaginismus [13, 14, 50, 51], and 4 to BoNT injections for vulvodynia [52-55]. We subdivided the results for each pelvic disease and summarized the studies in chronological order in the **Table 1**.

CHRONIC PELVIC PAIN

Of the four studies describing the use of BoNT in treating chronic pelvic pain syndromes two were case report studies [46, 48], one was an open-label study [47], and one a doubleblind, placebo-controlled randomized study [49] (**Table 1**).

The first case report study was an early study from our group describing 2 women with chronic genital pain syndromes, in whom needle EMG documented pelvic floor muscle spasms. After we injected BoNT-A (20 to 40 mU of Dysport) into two sites in the levator ani (LA) muscle, pelvic floor pain and muscle spasms improved and symptom relief lasted from few days to several months [46]. From a technical viewpoint we underline that in our study [46] EMG guidance allowed us to identify the right muscle to inject and observe muscle hyperactivity.

In the second case report, by others, a woman with pelvic pain and spasm documented by a high manometry value (48 cm H20, normal value of vaginal resting manometry is<40 cm H20) responded well to BoNT-A treatment [48].

The third study we identified dealing with chronic pelvic pain syndromes was an open-label pilot-study, conducted in 12 women who had suffered from pelvic pain and muscle hypertonicity (defined as a vaginal resting manometry reading of > 40 cm H20) for at least 2 years. After BoNT-A (Botox, 40 mU) was injected into the puborectalis and pubococcygeus muscles bilaterally, manometric resting pressure decreased, dyspareunia and dysmenorrhea, assessed by means of a visual analog scale (VAS), diminished and sexual activity scores increased. Nonmenstrual pelvic pain and dyschesia did not decrease significantly. These results remained unchanged when Botox was injected at various dilutions (10, 20 and 100 mU/ml). Follow-up assessment at 3 months disclosed the following adverse effects: influenzalike syndrome (2 women), mild urinary leakage (1 woman) and increased flatus (2 women) [47].

The fourth study dealing with chronic pelvic pain syndromes was the only double-blind, randomized, placebocontrolled trial so far conducted to assess whether BoNT-A is more effective than placebo in reducing pain and pelvic floor pressure in women with chronic pelvic pain and pelvic floor muscle spasm [49] . All participants presented with chronic pelvic pain of more than 2 years duration and evidence of pelvic floor muscle spasm. Thirty women had 80 units of BoNT-A injected into the pelvic floor muscles, and 30 women received saline. Dysmenorrhea, dyspareunia, dyschesia, and nonmenstrual pelvic pain were assessed by VAS at baseline and then monthly for 6 months. Pelvic floor pressures were measured by

vaginal manometry. After 2 weeks dyspareunia decreased significantly in both groups (patients, VAS score 66 versus 12; chi-square test = 25.78, P < .001; placebo, VAS score 64 versus 27; chi-square test= 2.98, P = .043). Non-menstrual pelvic pain decreased only in the BoNT-A group (VAS score 51 versus 22; chi-square test = 16.98, P = .009). Pelvic floor pressure (centimeters of H2O) in the BoNT-A group diminished significantly from baseline (VAS score 49 versus 32; chi-square= 39.53, P < .001), and the placebo group also had lower pelvic floor muscle pressures after treatment than at baseline (VAS score 44 versus 39; chi-square test= 19.85, P = .003). Women underwent a single treatment session were followed for 26 weeks after injections. Two women became pregnant in the BoNT-A group, and two reported urinary incontinence.

In chronic pelvic pain, the only double-blinded study [49], confirms the results reported in case reports in showing the efficacy of BoNT-A in decreasing pain in women. The fact that none of the other reported studies [47-49] used EMG guidance technique may explain why our patients had benefit with a lower BoNT dose [46]. Nevertheless, presumably because we injected a lower BoNT-A dose than others [47-49] (Dysport 20-40 mU vs Botox 40-100 mU), our patients' benefits were shorter lasting and adverse effects were less severe in our patients [46] than in those of patients treated by Abbott et al. [49] and the others [47,48].

VAGINISMUS

Of the four studies we identified describing the use of BoNT injections in treating vaginismus two were case report studies [13,14], one was an open-label trial [51] and the fourth was an open-label placebo-controlled study [50].

The first available case report study showed that a woman with LLV and interstitial cystitis benefitted from BoNT-A injected into the LA muscle under EMG guidance and the benefit lasted two years [14].

The second study our search identified was a recent case report by our group describing a patient with coexisting idiopathic cervical dystonia and LLV who received benefit from BoNT-A injected into the LA muscle under EMG guidance. BoNT reduced vaginismus, normalized the patient's sexual intercourse and re-injections every three months maintained the benefit [13].

The third study we identified was a controlled, open-label placebo-control trial conducted in eight women with LLV all of whom were injected with BoNT-A into each of the two bulbospongiosus muscles [50]. After BoNT-a injections vaginismus improved and intercourse normalized. No patient needed re-injection and none of them had recurrent episodes of vaginismus during the 10 month follow-up. BoNT-A injections effected cure in all of the vaginismus patients with no complications or recurrence.

An open-label study conducted in recent years [51] recruited 24 women with third-to-fourth-degree vaginismus who had previously received unsuccessful treatments. Postinjection vaginal examination at 1 week showed that of the 24 recruits, 23 patients (95.8%) had little or no vaginismus, 18 (75%) achieved satisfactory intercourse after the first injection, 4 (16.7%) had mild pain, 1 was cured after a second injection, 1 patient refused vaginal examination and did not attempt to have coitus, and another had no coitus because her husband suffered from secondary impotence. A mean of 12.3 months (range 2-24 months) follow up disclosed no cases of recurrence [51].

These findings receive support from our own unpublished experience on BoNT injections for vaginismus. During the past four years, in an experimental study on the use of BoNT-A in pelvic floor disorders we have been treating 37 patients, aged 34.3± 9 years (mean±SD), with primary idiopathic LLV, all of whom were previously treated with conventional psychosexual behavioural therapy. Patients who had coexisting vulvar vestibulitis, caused by introital trauma during attempted intercourse and consequent chronic vestibular inflammation, received antidepressants, GABAergic inhibitors and antimycotic drugs. Patients in whom these multimodal treatments induced no effective long-lasting benefit were then referred for EMG evaluation and BoNT treatment. EMG activity from the LA was analyzed and the patients in whom EMG recordings showed muscular hyperactivity at rest and reduced inhibition during straining were included in the study. We injected BoNT-A (Dysport, 20-40 mU) under EMG guidance in the LA muscle, in one site. In 20 of the 37 patients (54.5%) BoNT-A decreased EMG hyperactivity and improved vaginismus, restoring a normal sexual life after 2.58± 0,4 (mean ±SD) treatment cycles. Of the 37 patients initially recruited, 9 patients (24.3%) recovered from vaginismus and sexual intercourse had normalized but are still receiving treatment after 2.8 ±1.3 cycles. Of the 37 patients, 5 received no benefit and dropped out, 3 were lost to follow-up The BoNTA- induced benefit lasted an average 90 days. Two patients become pregnant after the study. None of the patients reported experiencing adverse effects [unpublished data].

In vaginismus, BoNT-A improves pain and intercourse [13,14,50,51], and open-label and controlled trials [50,51] induces a long-lasting benefit in all patients.

The effect duration seemed to depend on the dose, the higher the dose, the longer the benefit. Because we injected BoNT under EMG guidance we correctly localized the hypertonic LA muscle and therefore used a lower dose than others

[50,51]. Because we used lower BoNT-A doses, however, periodic re-injections were needed in about 25% of women and not all patients improved.

VULVODYNIA

Of the four studies we identified describing the use of BoNT injections in treating vulvodynia two were case report studies [52,53], one was an open-label study [54] and one an open-label dose escalation study [55].

The first study described a patient with refractory vulvodynia in whom severe dyspareunia was successfully managed with a novel therapeutic approach combining BoNT-A and surgery [52].

The second study described 2 women with vestibulodynia and treated with BoNT-A at 12-week intervals into the LA muscle [53]. Outcomes included VAS, weekly coital pain diaries, surface electromyography (sEMG) and a vulvar algesiometer. BoNT-A slightly reduced coital pain in 1 patient and was ineffective in the other. Pelvic floor hypertonicity and variability were markedly reduced in both patients, but vestibular hyperalgesia remained almost unchanged. The patient with greater pelvic floor tension had the largest reduction in diary-rated coital pain 2 weeks after the injection (29% vs. 9%) and on the VAS at 12 weeks (15% vs. 3%). In this case report study BoNT-A injections seemed to reduce LA spasms despite having little effect on vestibular allodynia [53].

The third study was an open-label, dose-escalation, pilot study and included 19 women with vestibulodynia [54]. The primary outcome measure was a standard numeric pain rating scale ranging from 0 to 10. Secondary measures were improvements in quality of life and change in medication use. Thirty days after treatment, the 7 patients who received 35 units of BoNT-A changed baseline pain scores (0-10) from 8.1 ± 0.70 (mean ±SD) to 2.9± 1.17. The benefit lasted 8 weeks, and none of the patients reported adverse effects. The 12 patients who received 50 units of BoNT-A changed their baseline pain score from 7.4 ±0.10 to1.8 ±0.72. The benefit lasted 14 weeks, and none of the patients reported adverse effects. BoNT-A injections also brought about a significant improvement in these patients' medication use and quality of life. BoNT-A reduced vulvodynia and the higher was the dose, the longer the benefit lasted.

The fourth study, conducted by Yoon et al [55] , was an open-label study of seven women with genital pain resistant to conventional pain managements. Each received 20 to 40 mU of BoNT-A injected into the vestibule, LA muscle or the perineal body. In all patients, BoNT-A resolved the pain. Five patients needed to be injected twice 2 weeks later and the other two patients needed only one reinjection. None of the patients reported adverse effects. The subjective pain score improved from 8.3 to 1.4, and none of the patient had recurrent genital pain during a 4 to 24 months (mean 11.6 months) follow-up. In this study BoNT induced a persisting improvement in vulvodynia.

In general data are concordant in showing a benefit of BoNT-A in improving vulvodynia. BoNT injections probably induce the best outcome in patients with vulvodynia who have coexisting life-long vaginismus, Most patients had periodic 12-14 weeks benefit from BoNT injections, some patients had permanent benefit.

VULVAR VESTIBULITIS SYNDROME

Our systematic search found no published studies using BoNT-A for the treatment of pain and spasm frequently associated with this disease. In our personal unpublished experience in clinical practice we enrolled 39 for study patients with VVS accompanied by acquired vaginismus, treated them with BoNT-A injected into the LA muscle and followed them for 4 years. In all the patients selected for study, EMG recordings of activity from the LA muscle showed muscular hyperactivity at rest and reduced inhibition during straining. The patients were treated with repeated cycles of BoNT-A (Dysport, Ipsen) injected into the LA muscle under EMG guidance and afterwards underwent EMG monitoring. When the study began and after each cycle all women completed VAS assessment for local pain (nonmenstrual pain, dysmenorrhea and dyspareunia), and a questionnaire relating to quality of life and bladder and bowel symptoms. 23 patients had constipation and 10 patients had urinary infections and micturition difficulty. Of the 39 patients treated, 24 (61.53%) completely recovered from VVS, had improvement in VAS from 8.2 ±1.2 (mean ± SD) to 2.8 ± 1.6, and sexual intercourse, micturition and their bowel movements normalized after 2.7 ± 0.22 treatment cycles. Conversely, 9 patients (23.07%) since the first injection recovered from VVS, had improvement in pain and sexual intercourse, micturition and bowel movements normalized but they still needed periodic BoNT-A reinjections after 4.33± 0.86 cycles. Of the 39 patients treated, 6 (15.38%) were lost to follow-up after two (mean 2.16 ±1.07) cycles, 5 patients for unknown reasons and 1 patient because she complained that she received no benefit in vulvodynia or spasms and still could not have sexual intercourse.The mean BoNT-A dose (0.1ml, 20 mU) used for each session was 0.12±0.06 ml; the benefit began from 3 to 20 days after the first BoNT-A injection. The mean interval elapsing between sessions was 3.1± 1.2 months. None of the patients reported adverse events but one patient reported transient urinary incontinence. After BoNT-A injections, EMG of the LA and EAS muscles showed reduced baseline hyperactivity and paradoxical activity with straining.

BoNT-A effectively resolved VVS accompanied by vaginismus because it reduced pelvic floor muscle hyperactivity and local pain. Our limited personal experience suggests that BoNT-A can effectively improve VVS in most patients. In some cases (about 25% in our study), reinjections may be needed to maintain the benefits.

DISCUSSION

Our review provides up-to-date evidence that BoNT-A, used since 1997 as therapy in women with pelvic floor disorders and genital pain, effectively improves chronic pelvic pain, vaginismus and vulvodynia/vulvar vestibulitis [13, 14-46, 55].

Despite the 50 patients referred by gynecologists to specialized centers such as our neurophysiologic academic center every year for detailed investigation of pelvic floor disorders and genital pain because many patients remain unsuccessfully treated with the more traditional therapy [4], we found relatively few published studies on the use of BoNT-A in these disorders. This expected result probably depends largely on the fact that many patients are reluctant to seek help from a specialist and physicians tend to neglect these disorders considering them of mental origin [55-58]. Another explanation is that because these disorders continue to raise diagnostic controversies no general therapeutic guidelines have yet acquired consensus nor have those for BoNT injections been drawn up.

For several years now we have used BoNT injections in managing pelvic disorders. This management choice now receives confirmation from our evidence-based review showing that BoNT-A improves pelvic floor disorders and genital pain in most patients, and that the benefit is long lasting , from about 3 to 6 months in chronic pelvic pain to about 2 years in vaginismus [14, 50, 51]. BoNT-A enhances quality of life [49] thus allowing yearned pregnancies [49], and probably reduces patients' social costs.

All patients with idiopathic chronic pelvic pain originating from LA muscle spasm can achieve benefit from treatment with BoNT-A, before traditional therapy . Patients with vaginismus might fare best from a multidisciplinary approach including conventional behavioral & psychosexual therapy, BoNT treatment, oral medication and biofeedback. Patients with phobic rather than dystonic vaginismus reap no benefit from BoNT injections and should probably be otherwise treated [18]. Patients with vulvodynia who report the greatest benefit from BoNT injections are probably those with a hyperactive pelvic floor, either lifelong (associated with vaginismus) or secondary to chronic introital inflammation. If patients with pelvic floor hyperactivity and vulvodynia benefit most from BoNT, a detailed clinical history and thorough physical examination should enable the physician to select the subset of patients who might benefit most from BoNT-A injections. For patients with VVS in whom a multimodal approach is planned, a targeted diagnostic work-up should also help define the best timing during the disease for BoNT-A injections.

To reduce possible BoNT-induced adverse events and ensure persisting benefit, we suggest starting BoNT-A injections in women with pelvic floor disorders at the lowest clinically effective doses [13, 14, 46] followed in later sessions by the highest doses [48, 49, 51]. The benefit obtained with BoNT injections seems independent on dilution [47]. To lower the BoNT doses injected, before choosing injection sites, we recommend localizing the hypertonic LA muscle to inject accurately under EMG guidance [13,46] .

Among open questions remaining about the benefit of BoNT-A in pelvic floor disorders and genital pain, the first is whether patients improve permanently. Our unpublished data on vaginismus and VVS suggest that about 65% of patients receive permanent benefit. The second open question is whether BoNT-A injections into the LA muscle improve not only chronic pelvic pain, vaginismus and vulvodynia/VVS, but also associated disorders such as constipation and urinary difficulties. Case report studies [13,14] and our unpublished data both report that BoNT-A injected into the LA muscle improves these disorders. BoNT-A injections into the puborectalis muscle improves constipation due to paradoxical muscle contraction in the puborectalis syndrome and anismus [59, 60]. No trials have yet addressed therapeutic benefits of BoNT in comorbidity.

FUTURE RESEARCH

Controlled trials are necessary to define better the efficacy of the BoNT in vaginismus, and vulvodynia /VVS and to identify the subset of patients who could get the maximum benefit. Larger patient groups and longer followup studies (about 5 years) could provide information on which pelvic conditions require re-injections in women and identify the subset of patients who could fare best from this relatively novel approach. The major areas of uncertainty to be investigated in controlled trials are vulvodynia and VVS.

Recent evidence on the hyperactivity of the pelvic floor and comorbidity with dyspareunia and vaginismus in women with interstitial cystitis suggests that this condition could now be included among the indications for BoNT therapy [61-63].

Collectively, current knowledge favors using a multimodal approach to the treatment of chronic pelvic pain, vaginismus, and vulvodynia / VVS seeking consensus guidelines.

Strategies are needed to encourage women seek their physicians' advice and to help specialists become familiar with the use of BoNT for the treatment of genital dysfunctions and pain.

CONCLUSIONS

BoNT-A -- already used since the 1980s for strabismus, dystonia and spasticity -- has over the past 10 years enjoyed increasing use also for pelvic floor disorders and genital pain. Notwithstanding the relatively few publications available to date the current medical literature suggests that BoNT-A effectively improves chronic pain syndromes, vaginismus, and vulvodynia/VVS. The encouraging preliminary results suggest that BoNT-A is an efficient tool for treating pelvic floor disorders as the only therapy or in a multidisciplinary treatment approach. BoNT-A therapy merits more widespread use in women with pelvic floor disorders and genital pain because it improves symptoms, enhances quality of life and probably reduces social costs BoNT-A.

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Table 1. Included Studies

Disease	Study (First Author, Year)	Participants	BoNT Type, Dose, Injection Sites, Muscle Injection Technique	Results, Effect Duration, Cycles	Comments AE
Chronic pelvic pain	Romito et al. 2004 [46]	2 patients	Dysport 1 patient, 10 mU x 2 1 patient, 20 mU x 2 LA, bilaterally EMG guided	↓ local pain 1 patient, 5 months, 1 cycle 1 patient, 6 months, 1 cycle	Case report No AE
	Jarvis et al. 2004 [47]	12 patients	Botox, 40 mU (10 mU x 4), 3 dilutions Puborectalis and pubococcygeus, bilaterally hand guided	↑ sexual activity ↓ dyspareunia and dysmenorrhea ↓ manometry resting pressure 3 months, 1 cycle	Pilot study 2 flu-like syndrome, 1 urinary leakage, 1 increased flatus
	Thomson et al. 2005 [48]	1 patient	Botox, 40 mU (10 mU 0,5 ml x 4) to 80 mU (20 mU x 4) Puborectalis and pubococcygeus, bilaterally hand guided	↓ dysmenorrhea ↓ dyspareunia ↓ dyschesia Every 4 months, 4 cycles Follow-up: 16 months	Case report No AE
	Abbott et al. 2006 [49]	30 patients 30 controls	Botox, 80 mU (20 x 4), 1 dilution Puborectalis and pubococcygeus, bilaterally hand guided	↓ Dyspareunia, both groups ↓ Nonmenstrual pain < treated group ↓ resting manometry, both groups, treated group < placebo ↓ Maximum contraction manometry, treated group 6 months, 1 cycle	Double-blinded, randomized, placebo-controlled 2 pregnant (treated group) 2 urinary incontinence (treated group)
Vaginismus	Brin and Vapnek 1997 [14]	1 patient	Botox, 10 UI (5 mU x 2) to 40 mU (20 mU x 2) Anterior vagina wall muscles, bilaterally EMG guided	↑ sexual Intercourses (none before BoNT) Within few days to 5 weeks->24 months, 2 cycles Follow-up: 2 years	Case report No AE
	Shafik and El-Siba 2000 [50]	8 patients 5 controls	BoNT-A, (50 mU) 25 mU x 2 LA (bulbospiongiosus) EMG guided	↑ sexual intercourses (none before BoNT) permanent, 1 cycle 10.2 ±3.3 months	Open label Placebo-control No AE
	Ghazizadeh and Nikzad 2004 [51]	24 patients	Dysport, 150-400 mU, 6 Puborectalis, bilaterally	18 patients, ↑ Sexual intercourse (none before BoNT) 4 patients, ↓ local pain 12.3 months (2 to 24 months), 1 cycle (24 patients), 2 cycles (1 patient)	Open label No AE
	Bertolasi et al. 2008 [13]	1 patient	Dysport, 20 mU x 1 LA EMG guided	↑ sexual intercourses ↓ local pain ↓ constipation 3 month re-injections follow-up: 2 years	Case report Associated cervical dystonia No AE
Vulvodynia	Gunter 2004 [52]	1 patient	BoNT-A, 20 mU LA	↓ local pain	Case report No AE Associated Surgery

	Brown et al. 2006 [53]	2 patients	BoNT-A 1 patient 20 mU 1 patient 40 mU LA	= hyperalgesia ↓ pelvic floor hypertonicitiy (sEMG) 1 patient, < coital pain 2 weeks to 3 months, 1 cycle	Case report No AE
	Dykstra et al. 2006 [54]	19 patients	BoNT-A 7 patients, 35 mU BoNT-A 12 patients 50 mU	↓ local pain ↓ oral medication ↑ QOL 2 months (50mU group), 1 month (35mU group)	Open label Dose-escalation No AE
	Yoon et al. 2007 [55]	7 patients	BoNT-A, 20-40 mU, vestibule, LA or perineal body	↓ local pain 5 patients, after 2 weeks, 2 cycles 2 patients, permanent, 1 cycle follow up: 24 months	Open label No AE

BoNT-A : botulinum neurotoxin type A

AE : adverse event

LA : levator ani muscle

↓ : decreased

↑ : increased

= : unchanged

QOL : quality of life