Medical Therapies for the Treatment of Overactive Pelvic Floor

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15.1 Introduction

The pelvic floor is a highly compact area comprised of muscles, tendons, ligaments, fascia, and nerves. Overactive or contracted musculature in the pelvic floor is associated with several conditions such as vulvodynia and urinary incontinence, as well as symptoms such as dyspareunia, pelvic pain, and urinary frequency for which patients seek medical intervention. A number of factors are associated with pelvic floor muscle overactivity including a history of recurrent vulvovaginal infections, prolonged sitting, postural dysfunction, history of traumatic labor and delivery, urogenital cancer, history of physical trauma (such as a fall onto the coccyx or pelvic fracture), anxiety, sexual abuse, and constipation. Overactive pelvic floor (OPF) is understood to be a multifactorial condition requiring a multidisciplinary medical, psychological, and physical therapy team. This chapter will focus on medical therapies for OPF and will summarize the evidence-based data regarding medical interventions available for the treatment of pelvic floor overactivity.

15.2 Relationship between OPF and Symptoms

An OPF is related to several possible presentations that physicians are likely to encounter in the clinical setting. Patients describing symptoms of pain, paresthesias, and other sensorimotor pelvic complaints may be suffering from compression of nerves such as the pudendal nerve or any of its branches (dorsal clitoral, perineal, inferior rectal). Other presentations related to OPF include introital dyspareunia, pain with speculum insertion, urinary frequency, the sensation of incomplete emptying with urination, chronic constipation, and rectal fissures. In severe cases, pelvic floor muscle overactivity can cause nonprovoked, chronic vulvovaginal burning and pain (vulvodynia).

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15.3 Medical Assessment

Any evaluation of potential OPF should begin with a thorough history. Patients should be questioned about any of the following symptoms: vulvovaginal burning, throbbing, aching, soreness, introital dyspareunia, vaginal dyspareunia, urinary frequency, sensations of incomplete emptying with urinary, constipation, hemorrhoids, rectal fissures, pain with defecation, injury to the sacrum or coccyx, and injury to the lower back or hips. In addition, patients should be asked if they have a history of "holding urine," aggressive core muscle strengthening exercises, and a history of physical, emotional, or sexual abuse. Affirmative responses to any of these symptoms can be suggestive of OPF.

15.4 Physical Assessment

A brief screening exam can identify the majority of women with OPF and other types of pathologies that are frequently co-morbid with OPF. A description of this exam is as follows: a sensory exam of the vulva is performed using a moistened cotton swab to determine if there are areas that exhibit an abnormal pain response. Women with sexual pain can exhibit allodynia (i.e., the perception of pain upon provocation by a normally nonpainful stimulus such as being touched with a cotton swab) or hyperpathia (i.e., pain provoked by very light touch). This exam should be performed systematically to ensure that all areas of the anogenital region are tested. Initially, the medial thigh, buttocks, and mons pubis are palpated. These areas are typically not painful and this allows the patient to get comfortable with this exam [1]. The labia majora, clitoral prepuce, perineum, and interlabial sulci should then be palpated. Pain in these areas would suggest a process that is affecting the whole anogenital region including vulvar dermatoses, vulvovaginal infections, or neuropathic processes such as pudendal neuralgia. The labia minora are then gently palpated. First, the medial labia minora are gently touched lateral to Hart's line, which is the lateral boundary of the vulvar vestibule. The cotton swab is then used to gently palpate the vestibule at five locations: at the ostia of the Skene glands (lateral to the urethra), at the ostia of the Bartholin glands (4 and 8 o'clock on the vestibule), and at 6 o'clock at the posterior fourchette. Patients with vestibulodynia experience allodynia with the cotton swab test confined to the tissue of the vulvar vestibule but have normal sensation lateral to Hart's line. If the pain is localized to the vestibule, it is important to determine if the pain affects the entire vestibule or just the posterior vestibule as pain throughout the entire vestibule is an indication that there is an intrinsic pathology within the mucosa of the vestibular endoderm whereas, pain confined only to the posterior vestibule suggests that the pain is due to OFP [2].

A manual exam is then performed with one finger (instead of the usual two). The examiner's index finger is inserted through the hymen without touching the vestibule. The finger is firmly pressed downward towards the rectum approximately 2 cm proximal to the hymen. This should elicit the symptom of "pressure" or the "need to defecate" but not pain. Once the patient is normalized to the sensation of pressure, the pelvic muscles are examined. Moderate pressure is applied sequentially to the following muscles: coccygeus, iliococcygeus, pubococcygeus, puborectalis, and obturator internus. When each muscle is palpated, the patient should be asked "is this pressure or discomfort?" In addition, evidence of taught bands, knots, tender points, and trigger points should be noted. Discomfort during this part of the examination is highly suggestive of OFP. Then the urethra and bladder trigone are gently palpated. Intrinsic tenderness of the urethra may be suggestive of a urethral diverticulum or interstitial cystitis, while tenderness of the bladder may be suggestive of either interstitial cystitis or endometriosis.

The ischial spine is then located and the pudendal nerve is palpated as it enters Alcock's canal. Tenderness of the pudendal nerve is suggestive of pudendal neuralgia. Next, a bimanual examination is performed to assess the uterus and adnexa. Abnormalities in the size, shape, or

contour may be indicative of a leiomyoma. A diffusely enlarged, "boggy" and tender uterus may be signs of adenomyosis. Enlargement of the adnexa may represent an ovarian mass, whereas tenderness of the adnexa can often be a sign of a sexually transmitted infection, pelvic inflammatory disease, or endometriosis. A rectovaginal examination is then performed to assess the rectovaginal septum and the posterior cul-de-sac. Thickening or nodularity of the septum, nodularity of the uterosacral ligaments, can be suggestive of endometriosis [1].

If the aforementioned history and physical exam are consistent with a diagnosis of OPF, a referral to a skilled pelvic floor physical therapist is warranted for a more thorough musculoskeletal examination. Medications may be used alone, or as adjuvant treatment in combination with physiotherapy. The authors typically start with diazepam suppositories (Sect. 15.4.2 below) and systemic muscle relaxants such as cyclobenzaprine (Sect. 15.4.3 below) and reserve botulinum toxin type A (BTTA) (Sect. 15.4.1 below) for patients with more recalcitrant OFP. However, there have been no evidence-based algorithms published, therefore, decisions on medications must be made by taking into account each patient's medical history and concurrent medications.

The following medications have been described for the use of OFP.

15.4.1 Botulinum Toxin Type A

Botulinum toxin type A (BTTA) (Botox, Allergan, Irvine, California) has been shown to decrease muscle-related chronic pelvic pain. It does so by interfering with acetylcholine release at the neuromuscular junction, resulting in a decrease in resting tone and maximal contraction ability of the injected muscle. Due to its effectiveness as a paralytic, it is employed for widespread indications such as cosmetic enhancement and hyperhidrosis control as well as for relief from pain of musculoskeletal disorders. In a 2009 review article, Abbott evaluated gynecological indications for BTTA injections for women suffering from chronic pelvic pain. With the few case studies and research prior to 2009, Abbott concluded that vulvar pain may be reduced for a period of 3–6 months in women with provoked vestibulodynia after 20–40 unit injections of BTTA. Furthermore, Abbott compared the benefit of BTTA injection with pelvic floor physical therapy in women with pelvic floor muscle spasm. Those who received BTTA injection appeared to have no significant improvement in pain compared with participants who underwent pelvic floor physical therapy. Therefore, pelvic floor physical therapy is appropriate as an initial, minimally invasive intervention. However, if pain continues to persist despite pelvic floor physical therapy, BTTA injections are indicated as a next-step, more aggressive approach [3].

Another study explored the effects of BTTA on refractory myofascial pelvic pain [4]. Twenty-nine women participated in the study. Patients reported pain during digital palpation of the pelvic floor muscles using the 0–10 pain scale before and after levator ani BTTA injection (100–300 units). Seventy-nine percent of the participants reported improvement in pain on palpation post treatment, and 15 participants elected to undergo a second treatment, an average of 4 months after original injection. Few adverse side effects such as fecal incontinence, urinary retention, constipation and/or rectal pain were reported, all resolved spontaneously [4].

Moldwin and Fariello [5] analyzed the benefit of various myofascial trigger point (MTrP) injection therapy techniques, including BTTA, in treating urological pain syndromes. MTrPs are painful taut muscle bands (also known as "knots") that may create local and/or referred pain. The authors described three types of injection options to treat MTrPs, the first of which was a BTTA injection. The second group of women received intramuscular infiltration with a local anesthetic, lidocaine to deactivate MTrPs and to provide immediate pain relief. Lidocaine has been shown to have effects lasting from several hours to weeks and provide analgesic effect spreads to the tissue surrounding MTrPs, adding

additional therapeutic affect. The last approach, dry needling, involved fine acupuncture needle penetration into the tightest, most painful muscle fibers. All three approaches provided therapeutic benefit in the treatment of urological pain-related disorders with no statistically significant difference [5].

Finally, a study by Nesbitt-Hawes et al. [6] analyzed the benefit of single vs. multiple BTTA injections. Their study included 37 women between the ages of 21 and 52 who presented with at least two out of three criteria: pelvic floor muscle pain upon palpation, vaginal manometry pressure of greater than 40 cm H_2O and chronic pelvic pain. Pain was rated on the visual analogue scale (VAS) regarding dysmenorrhea, dyspareunia, dyschezia, and nonmenstrual pelvic pain. Pelvic floor manometry was performed with an air-filled vaginal probe. All 37 participants were administered 100 IU of BTTA diluted in 4 mL of normal saline. The BTTA was injected into two muscles: the pubococcygeus and puborectalis, bilaterally. Follow-up VAS and manometry assessments were performed at 4, 12, and 26 weeks after the initial injection. Twenty-six participants required only one injection. The remaining 11 participants were offered reinjections when their pain returned following an initial period of remission.

Of the women who received multiple injections, no major adverse side effects were reported. Furthermore, there appeared to be a cumulative effect of both decreased vaginal resting tone and maximal contraction strength. One woman reported vulvar irritation after her initial injection, and 23 women (35 %) reported flu-like symptoms during the 26-week follow-up period. There was no reported incidence of urinary or fecal incontinence. In addition, the researchers did not encounter the same antibody development that was observed in nongynecological BTTA studies, probably due to lower dosages (100 IU vs. ~6000 IU) and longer treatment intervals (>3 months vs. <3 months). In conclusion, multiple injections of BTTA are just as effective as the initial injection, and it is an appropriate treatment should pain return [6].

15.4.2 Diazepam Suppositories

In contrast to BTTA's paralytic properties, diazepam is a benzodiazepine drug that works as a skeletal muscle relaxant, anxiolytic, anticonvulsant and sedative, by enhancing the effects of the inhibitory GABAneurotransmitter. Its widespread effects have made it a drug of choice for many conditions including muscle pain, anxiety, seizures and alcohol withdrawal.

Recently, researchers have begun to explore the effect of diazepam on pelvic floor muscle dysfunction. In a 2010 retrospective study by Rogalski and colleagues indicated that vaginal diazepam suppository usage in high-tone pelvic floor dysfunction, in conjunction with pelvic floor physical therapy and trigger point injections, significantly helped relieve discomfort from pelvic pain. The researchers reviewed charts of 26 women who suffered from bladder pain, dyspareunia and hypertonicity of the levator ani muscles. Sexual dysfunction, including dyspareunia was measured with the Female Sexual Function Index (FSFI) and pain was assessed with a Visual Analog Scale for Pain (VAS-P). Twenty-five of the 26 participants reported subjective improvements, and six out of the seven sexually active patients were able to resume intercourse after suppository usage. On average, VAS-P levels decreased 1.44 on the 10-point scale [7].

In contrast, a 2013 study by Crisp et al. indicated that there is little to no benefit of intravaginal diazepam suppository in decreasing pelvic floor muscle resting tone. However, unlike the Rogalski study discussed above, women in this study were not allowed to use adjuvant treatments such as physical therapy, biofeedback, or trigger point injections. In this triple blinded placebo-controlled randomized trial, 21 women (average age 36.1 years old) with elevated pelvic floor EMG muscle resting tone (greater than or equal to 2.0 μV) were administered either 10 mg diazepam suppository or placebo for 28 consecutive nights. Outcome measures included vaginal surface EMG measurements, FSFI, the Short Form Health Survey 12 (SF-12) VAS, and the

patient Global Impression of Severity (PGI-S) and Improvement (PGI-I). After 4 weeks, no difference was seen regarding the EMG resting tone between the study and control groups, nor were any significant differences detected on the survey results. Consequently, the results of the study indicate that vaginal diazepam suppositories used in isolation, without any other treatment modalities, do not improve pelvic floor muscle resting tone [8].

15.4.3 Cyclobenzaprine

Cyclobenzaprine is a muscle relaxant whose mechanism of action is hypothesized to affect the alpha and gamma motor neurons of the central nervous system to decrease muscle spasm. Shekh and Kunka [9] performed a case study involving using cyclobenzaprine to treat a 26-year-old male who presented with a levator ani syndrome (LAS) symptoms of severe, episodic aching anorectal pain lasting 30–60 min, one to three times a day for 3 weeks. Other causes such as lesions, hemorrhoids, and anal fissure were ruled out. The patient was treated three times daily with 5 mg of cyclobenzaprine for 1 week and reported complete resolution of pain after only 3 days of treatment. The patient continued to remain symptom-free at the 6-month follow-up visit. The only adverse effect reported while on cyclobenzaprine was mild drowsiness, which spontaneously resolved upon discontinued use [9].

15.4.4 Topical Nitroglycerin and Topical Diltiazem

Nitroglycerin has been used for the past 130 years as vasodilator, especially to treat angina pectoris. Nitroglycerin is converted into nitric oxide by the enzyme mitochondrial aldehyde dehydrogenase and is available in multiple forms, including sublingual tablets, patches, sprays, and creams. More recently, nitroglycerin has been demonstrated to reduce musculoskeletal pain through its effects as a vasodilator. A literature review performed in 2011 by Garrick concluded that topical nitroglycerin (TN) significantly helps decrease pain due to acute tendon injuries [10].

Furthermore, Hashmi, Memon, and Khan [11] concluded that TN is an effective medication for chronic anal fissures, frequently caused by spasm of the anal sphincter and puborectalis muscle, and it should be included as a first line of treatment. Their prospective experimental study included 46 women and 46 men, with mean age of 30. Treatment consisted of application of 0.2 % topical TN for 8 weeks. Upon completion of the 8th week treatment period, 76 participants demonstrated anal fissure healing, whereas the remaining 20 participants demonstrated partial improvement in symptoms or nonhealing. The most common side effect reported by 21 participants was headache [11]. In addition, Mari et al. [12] compared the benefit of TN versus lidocaine in treating postoperative pain and anorectal muscle spasm after stapled hemorrhoidopexy procedure. In their single blind, parallel group, randomized controlled trial, the researchers randomly assigned participants to receive twice daily, topical application of either glyceryl trinitrate 0.4 % ointment or lidocaine chlorohydrate 2.5 % gel for 14 days. Pain intensity was measured on the VAS and was reported by participants on days 2, 7, and 14. On all three occasions, average pain scores were lower in the group treated with glycerin trinitrate compared to the group treated with lidocaine (Day 2: 2.5 ± 1.0 vs. 4.0 ± 1.1, $p < 0.0001$; Day 7: 1.4 vs. 2.8, $p < 0.0001$; Day 14: 0.4 vs. 1.4, $p = 0.003$). Furthermore, anal resting pressure was measured in both groups after 14 days of treatment, and the mean pressure was lower in the TN group (75.4 ± 7.4 mmHg vs. 85.6 ± 7.9 mmHg, $p < 0.0001$). The researchers concluded that TN is an appropriate intervention to alleviate poststapled hemorrhoidopexy-related pain and muscle spasm [12].

Another study conducted by Sajid, et al. [13] compares the benefit of topical TN vs. topical diltiazem (DTZ), a calcium channel blocker, to treat chronic anal fissures. In this systematic review,

the authors analyzed 481 patients from seven randomized controlled trials. 283 patients were treated with DTZ and 243 were treated with TN. The results revealed that both TN and DTZ were equally beneficial (RR = 1.10; 95 % CI = 0.90, 1.34; $z = 0.92$; $P = 0.36$); however, participants who were treated with DTZ demonstrated fewer headaches (RR = 0.39; 95 % CI = 0.24, 0.66; $z = 3.54$; $P < 0.004$) and recurrence (RR = 0.68; 95 % CI = 0.52, 0.89; $z = 2.77$; $P < 0.006$) [13].

In addition, Tsunoda et al. [14] performed an open-label, nonblinded, prospective study to assess the benefit of DTZ for the treatment of chronic anal fissures. They used The Short Form 36 Health Survey (SF-36) to assess quality of life changes before and 6 weeks after treatment. Participants also reported pain, bleeding, and irritation using numerical rating scales. After 6 weeks of treatment, 21 of the 30 participants (70 %) demonstrated healed fissures. These individuals also reported improvements in pain, health perception, and quality of life [14].

Despite the encouraging results of these aforementioned trials using diltiazem for anal fissures, there have been no published studies looking at its effectiveness as a treatment for vulvovaginal pain caused by pelvic floor dysfunction. It is possible to surmise, however, that since diltiazem helps anal fissure by relaxing the anal sphincter controlled by the puborectalis muscle, that it potentially could help relax other muscles of the pelvic floor.

15.4.5 Gabapentin

Gabapentin in an endogenous neurotransmitter which acts in part by modulating the action of glutamate decarboxylase (GAD) and branched chain aminotransferase (BCAT) to increase gamma-Aminobutyric acid (GABA) biosynthesis. Though approved to prevent seizures and as an anxiolytic, it is employed for many other uses including neuropathic pain. Gabapentin is recommended as a first line of treatment for diabetic neuropathy-related pain, central neuropathic pain, and postherpetic neuralgia. It is also used to treat anxiety disorders, bipolar disorder, restless leg syndrome, and insomnia. A retrospective study performed by Boardman et al. found topical gabapentin effective in women with vulvodynia. Participants had both generalized (37 %) and localized (63 %) vulvodynia, and were treated with 2–6 % gabapentin for at least 8 weeks. Average pain score decreased 4.77, from 7.26 to 2.49 on a ten-point pain scale, and the mean pain score among the 35 evaluable women was significantly reduced from 7.26 to 2.49. Approximately 80 % of participants experienced at least a 50 % reduction in pain. Furthermore, sexual function improved in the majority of the study group and all patients who had reported decreased participation in intercourse prior to treatment due to pain reported increased intercourse frequency post treatment [15].

Furthermore, gabapentin has been proven to be beneficial in other nongynecological, women's health-related musculoskeletal dysfunction. For instance, pre-operative usage of gabapentin has been shown to reduce post-operative pain in women undergoing total mastectomies due to breast cancer. Bharti et al. [16] performed a randomized controlled trial with 40 adult females, and participants were randomly assigned to study group (gabapentin 600 mg 2 h prior to surgery) or a control group (placebo). Not only did the group who received gabapentin report lower pain levels at 30, 60, and 120 min postoperatively ($p < 0.001$), they also required less intraoperative propofol during surgery compared to controls ($p = 0.009$) [16]. It is important to note however, this improvement is not evident in all types of surgery. Because men who undergo prostatectomy may develop pelvic floor muscle dysfunction or weakness following surgery, Deniz et al. [17] analyzed the effect of gabapentin administration prior to radical retropubic prostatectomy. They discovered that while post-operative pain scales were lower amongst those who received 900 mg of oral gabapentin 2 h prior to surgery, post-operative tramadol consumption at 24 h post surgery were similar [17].

15.4.6 Amitriptyline, Desipramine

Despite the limited use of topical amitriptyline, a tricyclic antidepressant (TCA), for treatment of gynecological disorders is a retrospective review of medical records was conducted by Poterucha et al. [18] to assess the potential benefit of topical amitriptyline (1–2 %) and ketamine (0.5 %) (TAK) for the treatment of rectal, perineal, and genital pain. The researchers amassed data from a single academic medical center in the United States and identified 1068 individuals who were treated with TAK between the January 1, 2004 and November 28, 2011. Of these individuals, 13 received treatment for rectal, perineal, or genital pain. One participant (8 %) reported complete relief after TAK application, six (46 %) reported substantial relief, four (31 %) reported some relief, and only two (15 %) reported no significant change. No significant adverse responses were noted [18].

Additionally, Pagano and Wong [19] performed a prospective study using topical amitriptyline 2 % in sorbolene cream on 150 patients with provoked vestibulodynia and dyspareunia. One hundred and two participants exhibited purely provoked vestibulodynia, and 48 participants suffered both provoked and unprovoked vestibulodynia. On average, participants had experienced symptoms for 4.7 years prior to inclusion in the study. Participants were encouraged to apply a pea-size volume of the cream to the vulvar vestibule twice per day for 3 months. Of the 102 participants in the first group, 84 participants (56 %) responded to treatment. 25 exhibited slight yet appreciable improvement, 44 exhibited moderate improvement, 15 (10 %) exhibited an excellent response defined as completely pain-free intercourse. The response rate was similar in the participants who experienced both provoked and unprovoked vestibulodynia, with 48 % reporting positive response to treatment [19].

Leo and Dewani performed a literature review regarding the effectiveness of oral antidepressant medication in treating vulvodynia. The study included two randomized controlled trials, 1 quasi-experimental trial, 7 nonexperimental studies, and 3 case reports. The majority of the 13 reports involved TCA treatment. The authors concluded that there was a lack of sufficient evidence to support the utilization of antidepressant medication for vulvodynia treatment. Additional research is warranted to identify which patients who present with vulvodynia are the most appropriate candidates for antidepressant pharmacotherapy [20].

In addition, Foster et al. published a randomized controlled trial comparing the effects of topical lidocaine in isolation, oral desipramine in isolation, and a combination of lidocaine–desipramine. They conducted a 12-week randomized, double blind, placebo-controlled trial with 133 participants. The outcome measure used was the level of pain reported during tampon insertion. At the end of the treatment, no significant difference was noted between all three intervention groups (both monotherapies as well as the combined therapy group), as compared with the placebo group [21].

15.4.7 Selective Norepinephrine Reuptake Inhibitors

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) increase extracellular serotonin and norepinephrine in the central nervous system thereby helping to treat both depression and neuropathic pain. Milnacipran, an SNRI, has shown to help decrease chronic neuropathic pain and fibromyalgia-related pain. In a study by Ohnami et al. [22], dorsal horn spinal application of milnacipran resulted in prolonged inhibition of C-fiber evoked field potentials after establishment of spinal long-term potentiation. This was accomplished by activation of both the noradrenergic system as well as the spinal 5-hydroxytryptaminergic system. Results of this study deepened prior understanding of the potential usage of SNRI to treat chronic pain, suggesting further possibilities of SNRI treatment for chronic pain secondary to pelvic floor dysfunction [22].

Giannantoni et al. [23] studied duloxetine, another SNRI, in the treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men. The outcome measures utilized to measure

improvement were the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), the International Index of Erectile Function-5 (IIEF-5) questionnaire, uroflowmetry and the Hamilton Anxiety Scale (HAM-A) and Hamilton Depression Scale (HAM-D) to assess psychological status. Measurements were performed immediately after drug administration as well as 16 weeks post treatment. In this randomized controlled trial, the study group received multimodal treatment which included tamsulosin, saw palmetto and duloxetine (60 mg/day), whereas the control group received treatment consisting of equal amounts of tamsulosin and saw palmetto. At the 16-week follow-up assessment, NIH-CPSI pain, quality of life, and total subscores, as well as HAM-A and HAM-D were significantly improved in the study group compared to controls. The researchers concluded that the use of duloxetine, in conjunction with alpha-blocker medication and saw palmetto extract, enables improved CP/CPPS pain reduction, psychological well-being, and quality of life [23].

15.5 Conclusion

Pelvic floor overactivity rarely exists as an isolated condition and instead is related to several neurological, musculoskeletal, urological, oncological, gynecological, and gastrological presentations. As such, physicians in nearly all disciplines will encounter patients challenged with pelvic floor overactivity, which negatively impacts sexual functioning and quality of life. We have presented several options that physicians may consider in offering medical treatment regimens as part of a multidisciplinary approach to the treatment of OPF.

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