Evaluation of Female Sexual Dysfunction (FSD) and Anti-depressants Use

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Abstract

Introduction: We have previously reported that the addition of pentosan polysulfate (PPS) to a regimen of anti-depressant medication for the treatment of Painful Bladder Syndrome (PBS) failed to improve patient symptom scores, evaluated by the Female Sexual Function Index (FSFI). Herein, we report on 1300 subjects indexed by the use anti-depressant medication and further indexed by both the class of anti-depressant and PPS use. The degree of FSD associated with the disease was then compared.

Methods: Domain values were obtained using the FSFI. The respondents were indexed first by the use of anti-depressant medication and then by the class of such medication (Tricyclic antidepressants (TCA), Selective serotonin reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs), Benzodiazepines, and Aminoketones), then further by the use of PPS.

Results: No differences in overall FSFI was observed among the 5 classes of anti-depressant medication (NS). When the 6 domains of FSFI were examined no differences were observed in Arousal, Lubrication, Orgasm, Satisfaction and Pain. However, respondents taking Aminoketones had a significantly higher FSFI score in the domain of Desire than those taking TCA (p=0.016), SSRIs (p=0.016), SNRIs (p=0.03) and Benzodiazepines (p=0.04). The addition of PPS to the anti-depressant medication produced no patient benefit over that of the anti-depressants alone. The addition of PPS to Benzodiazepines significantly worsened pain from 1.61 ± 1.55 to 0.54 ± 0.51 (p=0.007)

Conclusions: The addition of pentosan polysulfate sodium (PPS) to a regimen of anti-depressant medication for the treatment of PBS failed to improve patient symptom scores, as evaluated by the FSFI.

INTRODUCTION

Painful Bladder Syndrome (PBS) affects more than one million women in the United States with symptoms encompassing urinary urgency, frequency, and pelvic pain with sexual dysfunction affecting as many as 25-30% of women [1-3]. PBS, as reported by Curhan et al., mainly affects middle aged women, albeit cases have been seen in the elderly, men, and in children [4]. It is considered a diagnosis of exclusion by the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases [5]. On average, patients live through symptoms for seven years before a diagnosis can be made [6].

We have previously reported that female sexual dysfunction is significantly worse in women with painful bladder syndrome when compared to control using the Female Sexual Function Index (FSFI), [7]. The FSFI is a self-report measure made up of a 19-item questionnaire that measures the six domains designed to account for the multidimensional nature of female sexual dysfunction [1]. In this study, the FSFI was administered to 100 patients with painful bladder syndrome compared to 131 healthy women and 128 patients with Female Sexual Arousal Disorder (FSAD) [1]. Patients with PBS were found to have sexual dysfunction in all domains assessed by the FSFI and, compared to the FSAD cohort, displayed significant differences in the domain of pain [7].

Pentosan Polysulfate is a heparin-like sulfated polysaccharide that functions by repairing damaged glycosaminoglycan layers and reducing the permeability of irritants to the bladder urothelium. It is the only FDA approved oral treatment of bladder pain associated with this condition [8]. In a meta-analysis preformed by Hwang et al., PPS was shown to be better in the treatment of pain, urgency, and frequency when
compared to placebo [9]. The current regimen is 100 mg orally three times daily with re-assessment at 3 months [8].

Amitriptyline, a tricyclic antidepressant, has also been used in the treatment of PBS at dosages between 10mg-100mg daily and was first reported by Hanno and Wein in 1987 [10]. Hertle and van Ophoven studied 50 patients in a prospective, randomized, placebo controlled, double blind study using the O’Leary-Sant IC symptom and problem index to determine Amitriptyline’s effects on functional bladder capacity, frequency, intensity of pain and urgency. The patients were started on an initial dose of 25 mg, and were then titrated weekly to a maximum dose of 100 mg daily as tolerated. After four months of treatment, a statistical difference was achieved in the domains of pain and urgency with mouth dryness being the most common side effect reported [11].

We report herein the data on 1300 patients indexed by the use of anti-depressant medication, and further indexed by both the class of anti-depressant and pentosan polysulfate sodium (PPS) use. The effects of pentosan polysulfate (Elmiron) compared to a regimen of anti-depressant medication (tricyclic antidepressants [TCA], selective serotonin reuptake inhibitors [SSRI], serotonin-norepinephrine reuptake inhibitors [SNRI], benzodiazepines, and aminoketones) were quantified using the FSFI to determine the degree of female sexual dysfunction in female patients with PBS. The degree of FSD associated with the disease was then compared. The majority of the literature has focused on PPS and TCAs and their respective effects on alleviating the symptoms of PBS.

PATIENTS AND METHODS

We administered the FSFI to female patients via an online web survey at the Interstitial Cystitis Network web page at: www.ic-network.com. The participants were not blinded to the fact that this study was examining the link between PBS and FSD. The data obtained from the questionnaire was then downloaded into a study database where it was updated weekly. Duplicated survey data was identified through a manual review of returned questionnaires, and discarded as appropriate. The data was analyzed on an item-for-item basis and by the six domains of FSD (desire, arousal, lubrication, orgasm, satisfaction, and pain). Each question in the survey was targeted to a specific parameter of FSD and the answers were rated on a Likert scale. The respondents were first indexed by their use of anti-depressant medications. They were further sorted by the class of each anti-depressant medication (Tricyclic Anti-depressants [TCA], Selective Serotonin Reuptake Inhibitors [SSRI], Serotonin-Norepinephrine Reuptake Inhibitors [SNRI], Benzodiazepines and aminoketones) and then further by the use of PPS therapy.

Determination of statistical significance was performed by analysis of variance (ANOVA) [12]. Post hoc comparison of individual concentration means with the control was completed using the Tukey-Kramer Multiple Comparison test [13], with all data reported as means with standard deviations [Tables 1,2].

RESULTS

A total of 1300 surveys were collected. After indexing by the use of anti-depressant medications, there were 325 surveys. The surveys were then further sorted by the class of each anti-depressant medication (Tricyclic Anti-depressants [TCA], Selective Serotonin Reuptake Inhibitors [SSRI], Serotonin-Norepinephrine Reuptake Inhibitors [SNRI], Benzodiazepines and aminoketones) and then further by the use of PPS therapy (Anti-Depressant + PPS n = 160 and Anti-Depressant + NO PPS n = 165). Of the 160 of respondents who reported the use of both Anti-Depressants and PPS, the mean age was 36.28 ± 11.52 years old and 95% of these surveys were from the United States. The use of Pain Medications was reported by 42.3%, 46.9% reported the use of medication for Overactive bladder, 15.5% reported the use of Birth Control and 13.1% reported being Menopausal. There were 165 of respondents who reported the use of Anti-Depressants with No PPS, the mean age was 38.04 ± 11.19 years old and 89.1% of these surveys were from the United States. The use of Pain Medications was reported by 35.8%, 29.7% reported the use of medication for Overactive bladder, 7.9% reported the use of Birth Control and 16.4% reported being Menopausal.

No differences in overall FSFI scores were observed among the five classes of anti-depressant medication (NS). When the six domains of FSFI were examined, no differences were observed in arousal, lubrication, orgasm, satisfaction, and pain (Table 1). However, respondents taking aminoketones had a significantly higher FSFI score in the domain of desire than those taking Tricyclic antidepressants (p= 0.016), SSRIs (p=0.016), SNRIs (p=0.03) and Benzodiazepines (p= 0.04). Table 2 further compares the data of those respondents taking only an anti-depressant medication across the six domains measured by the FSFI. The addition of PPS to the anti-depressant medication produced no patient benefit over that of the anti-depressants alone. In fact, our results show that the addition of PPS to Benzodiazepines significantly worsened pain from 1.61 ±1.55 to 0.54 ± 0.51 (p= 0.007).

DISCUSSION

PBS is a clinical condition characterized by urinary frequency, urgency, nocturia, and suprapubic (bladder and /or pelvic) pressure and pain [14]. While the etiology remains unclear, several pathogenic mechanisms have been theorized, including epithelial dysfunction, subclinical infection, mast cell and immune system dysfunction, vascular abnormalities, pelvic floor dysfunction and neurogenic inflammation [15]. The large degree of variation seen in the range, severity, and patient response to therapy suggest that multiple factors may be involved in the development of the disease. As a result many researchers have argued that a multi-modality approach should be employed in difficult cases, both for symptomatic relief and prevention of disease progression [15-17].

Currently PPS is the only FDA approved oral medication for the treatment of PBS [16]. The scientific rationale for the use of pentosan polysulfate as therapy for PBS is based upon the observation that most PBS patients have evidence of abnormal bladder epithelial permeability [16]. In one study Parsons et al instilled urea into the bladders of PBS patients and healthy controls and measured its concentration after 45 minutes, and found that the controls had only lost 4% compared to 25% observed in the PBS group [18]. Studies have failed to identify morphological differences between cases and controls, qualitative deficiencies in mucin components such as GP51 have been identified [19].
PPS forms a colloidal suspension that has been shown to bind to bladder epithelium in animal models; additionally it may act as a mast cell stabilizer [20]. In clinical studies, several long-term trials have supported PPS to be an effective treatment in PBS. Additional studies have shown the drug to be more beneficial the longer it is taken, and it can be coupled with hydroxyzine or antidepressants for symptomatic relief in refractory cases [21].

Anti-depressant therapy has become another widely reported pharmacologic treatment for PBS. TCA have multiple mechanisms of action, including inhibition of serotonin and norepinephrine reuptake, central and peripheral anticholinergic actions, and antihistamine effects. Additionally they have some anti-inflammatory effects, and believed to moderate the symptoms of PBS by increasing patient pain threshold [14]. Amitriptyline success rates as high as 64% to 90% have been reported, however it has never been tested in placebo controlled randomized trials [22,23]. To date no clinical trials have evaluated the benefit of benzodiazepines or other classes of anti-depressants. However, in a retrospective chart review of 26 patients with bladder pain, sexual pain, and levator hypertone, the addition of intravaginal diazepam suppository to a regimen of pelvic physical therapy and sexual modality therapy may prove beneficial in refractory cases, at least 50% of patients and anorgasmia in one third to half of patients treated [25,27,28]. Montejo-Gonzalez et al reported that only 25% of patients were willing to tolerate their sexual dysfunction, and women's degree of dysfunction was reported as more severe [27]. Unlike all other anti-depressants Bupropion, which has no direct serotonin agonist activity, is not associated with sexual dysfunction and animal studies have suggested that it may enhance both desire and orgasm [25]. Our results found that there was an increase in the domain of desire in patients taking aminoketones when compared to other anti-depressant classes.

Several case-control studies have reported a higher rate of mental health disorders in patients with PBS. Utilizing the Patient Health Questionnaire (PHQ), Novi et al., identified a higher rate of depression (OR 4.0) in 46 female cases when compared to age-matched controls [28]. Similarly, Weissman et al reported an odds ratio of 4.1 for the lifetime prevalence of panic disorder in 67 cases (56 women with IC/PBS and 11 men with CP/CPPS) [29]. Nickel et al found that patients with PBS reported significant sleep dysfunction, depression, anxiety and stress compared to asymptomatic controls. Moreover, catastrophizing pain was associated with decreased quality of life (particularly poor mental QOL) [31].

While many authors argue there is evidence that a multimodality therapy may prove beneficial in refractory cases,
concomitant treatment options have not been extensively evaluated. The results of our study reiterate our previous results, confirming that there is no overall benefit observed with combined anti-depressive therapy and PPS. Conversely, the sexual side effects associated with anti-depressants may instead serve to exacerbate underlying sexual dysfunction. Namely, benzodiazepines and concomitant PPS therapy were found in our study to significantly worsen symptoms of pain in patients with PBS.

These results may be explained by the fact that patients with PBS and co-existing anxiety or stress disorders treated with benzodiazepines represent a subset in the IC/PBS population. For example, several studies have suggested a possible medical syndrome previously linked to chromosome 13. In a case-control study, Talati et al reported that familial panic disorder and seasonal affective disorder were five or more times likely to report PBS symptoms and two times as likely to report mitral valve prolapsed and migraines [32]. In another study, Nishiğima et al analyzed the expression of beta-2 adrenoreceptor (ADRB2), which is abundantly expressed in detrusor muscle, and found a significant difference in the prevalence of the Arg16Gly polymorphism between IC patients and controls. Additionally, the polymorphism appeared to be more prevalent among Interstitial Cystitis patients in the TCA refractory group than in those who reported a good response to anti-depressant therapy [33].

While the large degree of variation seen in the range, severity, and patient response to therapy suggest that multiple factors are involved in the pathophysiology of the disease, it is possible that subgroups of differing etiologies may exist within the population. These subgroups may respond negatively to combined therapy. Careful consideration and observation should be applied before beginning multiple pharmacologic agents in the treatment of PBS.

No differences in overall FSFI were demonstrated among the five classes of anti-depressants alone. More specifically, when the six domains of FSFI were examined, no differences were observed in arousal, lubrication, orgasm, satisfaction and pain. However, there was a significantly higher score reported in the six domains of FSFI were examined. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000; 26: 191-208.

REFERENCES


