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Eradication of Long-Term Vaginismus Type of Genito-Pelvic Pain/ Penetration Disorder by Treating with Dextroamphetamine Sulfate

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ABSTRACT

There are many therapies for the vaginismus type of genito-pelvic pain/penetration disorder. However, as frequently found when there are multiple treatments for a given pathological disorder, not any of them are highly effective for this problem. It has been hypothesized that increased tissue permeability may be the etiologic factor causing inflammation in various tissues leading to a variety of different pain syndromes in various organ systems, including, but not limited to, the pelvis. Treatment with dextroamphetamine sulfate has resulted in significant palliation of the pain in the majority of cases treated. The hypothesized mechanism is that this amphetamine releases dopamine from sympathetic nerve fibers, which, in turn, diminishes excessive infiltration of irritants, which are the etiologic factor for the pain. Ideally, the best proof of efficacy for the treatment of this type of vaginismus/dyspareunia syndrome by dextroamphetamine sulfate would be to conduct a randomized prospective double-blinded multi-center study. However, because of the generic status of this drug, it is highly unlikely that any pharmaceutical company would fund such a study. The most practical feasible method to determine efficacy would be to try the drug on a very convincing cases of long-term severe vaginismus/dyspareunia syndrome that failed to respond to standard therapy. Indeed, such a case was found in a 32-year-old woman whose vaginismus was detected at puberty, that was associated with severe dyspareunia 10 years later, so that neither insertion of tampons nor intercourse had been possible. Within one month of treatment her vulvodynia/dyspareunia were eradicated. The relief has persisted for three years. Hopefully this case report may encourage treating physicians who treat a lot of similar cases to evaluate a large series or conduct a randomized study comparing amphetamine therapy vs. their best treatment option to date.

Keywords

Vaginismus, Dyspareunia, Dextroamphetamine sulfate, Increased cellular permeability syndrome.

Introduction

Dyspareunia is a persistent or recurrent pain with attempted or complete vaginal entry and/or pain with vaginal sexual intercourse [1]. Vaginismus is defined as persistent or recurrent difficulties to allow entry of a penis, finger, or any other object despite the woman's desire to have this type of insertion [1]. Recently it was decided that the defined differences between dyspareunia and vaginismus were too subtle so that they are no longer considered separate entities, but are now classified as genito-pelvic pain/ penetration disorder (GPPPD) [2].

In the psychiatric literature they define an entity of sexual pain/ penetration disorder (SPPD), which includes vaginismus, but excludes dyspareunia and vulvodynia which are classified as genitourinary disorders [3-5].

There are various causes of introital pain, and thus various treatments. Hill and Taylor summarize these treatment options as "avoiding vulvar irritants, using cotton underwear and pads, topical analgesics, estrogen, compounded or oral gabapentin, compounded muscle relaxants, amitriptyline, selective serotonin, or norepinephrine reuptake inhibitors, pelvic floor physical therapy, cognitive behavior therapy, and surgical excision [6-14]. Other treatments include sex counseling, psychotherapy, or botulinum toxin A (onobotulnum toxin A) [15-17].

There is evidence that many pain syndromes, including, but not limited to pelvic pain, are related to increased cellular permeability, with increased absorption into tissues of noxious, unwanted elements, leading to inflammation with subsequent pain [18]. This condition is known as the increased cellular permeability syndrome, which although very common, does not seem to be well known, based on the fact that most of the publications on the efficacy of using medication that negate the increase in cellular permeability and thus prevent inflammation and subsequent pain, seem to come from predominantly one treatment center [18-20]. Presently, the most effective drug, with the least side effects that is available on the pharmaceutical market, is dextroamphetamine sulfate [18-20]. The hypothesized mechanism of action is to increase the release of dopamine from sympathetic nerve fibers, and one of the functions of dopamine is to decrease cellular permeability [18-22].

There is evidence that the development of an inflammatory state in the uterus is important to help create spiral arteries by autoimmune removal of the thick walls of some of the uterine arteries, to create thin-walled spiral arteries that will enable nutrient exchange between mother and fetus [23,24]. In some instances excessive cellular permeability may not reach the critical level until the baseline defect is exacerbated by the further increase in cellular permeability by the suppressive effect of progesterone on dopamine secretion. Thus, excess cellular permeability leading to inflammation, and thus subsequent pain, may sometimes be restricted to the late luteal phase or during menses with the presence of dysmenorrhea [24,25]. However, sometimes the increased cellular permeability and subsequent inflammation, is present all month, but may be increased premenstrually or during menses [25,26]. Possibly, related to the small rise of progesterone before ovulation, or related to some other mechanism, there may be increased cellular permeability in the periovulatory time, leading to mittelschmerz [26]. Sometimes the pelvic pain syndrome manifests as dyspareunia, or includes dyspareunia with other symptoms, which may occur during the entire menstrual cycle, [27,28].

There is evidence that increased tissue permeability, leading to chronic inflammation, may be the main etiologic factor in causing pelvic pain of bladder origin (interstitial cystitis) as evidenced by a good response to treatment with the sympathomimetic amine dextroamphetamine sulfate, even when other standard therapies have failed [29,30]. Sometimes the interstitial cystitis may present as the sole manifestation, and sometimes it may be associated with other types of pelvic pain syndromes [28-30]. Sometimes the interstitial cystitis may be associated with other pain syndromes outside the pelvis, e.g., migraine headaches [28]. Generally, one will find not only great relief of the pelvic symptoms but also the extra pelvic pain [28]. Sometimes the cause of long-term abdominal pain is not clear if it is bowel or pelvic related, but yet good response to dextroamphetamine sulfate is found [31].

Other types of pelvic pain may be associated with extra pelvic pain syndromes, e.g., Crohn ‘s disease [26]. Dextroamphetamine sulfate has proven highly effective for treatment refractory inflammatory bowel disease presenting as the primary complaint, and not only improves the pain, but also the diarrhea [32-34].

Anecdotal case reports indicate that a given treatment can be highly effective, but does not provide the reader as to the percentage of cases that will respond. Though it is the experience of the authors of this manuscript, that amphetamine therapy is highly effective in the majority of cases of pelvic pain, the only large series was conducted by Paul Carpentier et al., and the data was presented at the American Society for Reproductive Medicine in 2020, which confirmed the efficacy of dextroamphetamine sulfate in a series of treatment refractory women with pelvic pain (mostly dysmenorrhea) [35].

From the standpoint of vestibular pain as the only manifestation of pelvic pain, there has been a case report of severe vulvovaginitis that began at age 8 in a girl who developed premature pubarche at age 7. She did not have menses, and the pain was constant without any probing. She also had attention disorder hyperactivity disorder (ADHD) and unexplained weight gain. Not only did the vulvar pain completely dissipate after initiating treatment with dextroamphetamine sulfate, but her ADHD markedly improved, and she lost weight [36]. Presented, herein, is the first case report of marked improvement of vaginismus type of GPPPD present since menarche following treatment with dextroamphetamine sulfate.

Case Report

A 32-year-old woman sought help for her main problem of vaginismus and vulvodynia that precluded her from having sexual intercourse with her male partner during their 6-year relationship. She stated that she had not been able to even insert a tampon since puberty.

Psychotherapy failed to improve the vaginismus, as did self-dilation attempts with her own fingers. Furthermore, amitriptyline did not help. Her main reason for consulting our group was to discuss future fertility methods since she was engaged and planned to be married within the year. She assumed that she would need in vitro fertilization (IVF) but wanted to know if monitoring of follicular maturation by abdominal ultrasound rather than pelvic sonography was possible. She was 61 inches tall and weighed 115 pounds, so we thought monitoring by abdominal ultrasound was possible. We also told her that we may be able to place a sperm laden intrauterine insemination catheter into her vagina at the time of peak follicular maturation, and thus avoid IVF.

She also had a history of dysmenorrhea, which was considered moderate, but not severe. In addition, she stated that for the last year she was plagued by a very annoying desquamative facial rash that only occurred premenstrually, and was diagnosed by dermatologists as psoriasis.

We suggested one more option for her future fertility, and that

was natural intercourse if we could eradicate the vulvodynia/vaginismus problem with treatment with dextroamphetamine sulfate therapy. After one month of 15mg dextroamphetamine sulfate immediate release tablets upon arising in the morning and at noon, her vulvodynia disappeared allowing her to use tampons and have painless intercourse. Her dysmenorrhea was no longer present, and she had complete eradication of the premenstrual rash. This improvement has persisted for 3 years, except for one month when the pharmacy substituted a different generic form of dextroamphetamine sulfate.

It should be noted that upon initial exam, the hymen was not imperforate, and the pain was strictly introital. A bimanual examination was not even attempted.

Discussion

In the one previous case report of improving dyspareunia with dextroamphetamine sulfate, the pain with intercourse was not introital, but only occurred with deep penetration [28]. Thus, we believe that this is the first case report of primary vulvodynia improved with dextroamphetamine sulfate. The very quick improvement suggests the pain was related to irritants infusing into the vulvar area causing excessive inflammation and pain, as opposed to a psychosexual etiology.

In her case, there was apparently a cellular permeability defect in her facial tissue, but the development of the skin lesions would only occur premenstrually related to progesterone suppressing dopamine release. Though the use of dextroamphetamine sulfate had been described almost 40 years ago to improve severe constant urticaria, and its benefit has been confirmed by other case reports and published series, sometimes urticaria may only occur premenstrually [37-40]. Amphetamines have also proven very effective is long-standing eczema [41].

Pelvic pain has responded quite well following amphetamine sulfate in patients documented to have endometriosis, or even adenomyosis, even where laparoscopic removal of endometrial implants resulted in no improvement of pain, or short-lived amelioration of pain, or improvement for a year or more [25,35,42-44].

A study by Yeung et al., using the more aggressive excisional technique for removing endometriosis, provides more insight into the role of endometriosis and the increased cellular permeability syndrome [44]. Repeat laparoscopy on teenage girls 2 years after excising their endometriotic lesions, not one girl was found to have a trace of endometriosis [44]. Yet 50% had return of their pain as severe as before laparoscopic surgery. This has suggested to us that the primary cause of pelvic pain in women with endometriosis is infiltration into pelvic tissues of irritating elements because of increased tissue permeability, and the presence of the endometriosis may be related to escape of menstrual tissue related to this permeability defect [24]. Nevertheless, the endometriotic tissue may exacerbate the permeability defect causing more irritants to infuse, besides the possibility of mechanical impingement on nerve endings [24]. Though endometriosis could have been present in the 32-year-old woman, we describe with moderate dysmenorrhea, and although the presence of endometriosis may be associated with dyspareunia after deep penetration, it was unlikely that its removal would have alleviated her main complaint of introital pain. Thus, her previous gynecologist and other consultants never suggested a laparoscopy. Thus, we believe that not only should dextroamphetamine sulfate be included in the treatment options for GPPPD, especially with dyspareunia, vaginismus, or vulvodynia/vulvovaginitis, but it should be considered first line therapy because of its safety and relative lack of side effects even in women trying to conceive who are already pregnant [24,45]. Obviously, more convincing would be the demonstration of marked improvement of vaginismus/dyspareunia in a well powered, multi-center, properly randomized (to placebo or alternate treatment) with dextroamphetamine sulfate. However, because the drug is a generic, it is highly unlikely a pharmaceutical company to provide funding for such a study. Thus, in our opinion the most practical method to at least prove that sympathomimetic amine therapy can be highly effective in some cases of vaginismus/dyspareunia syndrome is to find a very convincing case of long-term treatment refractory symptoms that responds quickly and effectively for a protracted time without losing efficacy. The case presented has all of the above qualifications.

It is hoped that this case report will generate interest in physicians or clinics with a large population of cases of vaginismus/dyspareunia to try treatment with dextroamphetamine sulfate to not only corroborate that this treatment can help this type of morbidity in some cases, but to find it efficacious with little or no side effects in the majority of women suffering from this condition.

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