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Case Report

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Increased Cellular Permeability Related to Relative Dopamine Deficiency May Play a Major Role in the Etiology of Dyspareunia by Causing Inflammation

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ABSTRACT

There are many possible causes of dyspareunia. There are many different proposed treatment modalities including psychotherapy, pelvic floor muscle physical therapy, and medications. Some medications aim to treat a specific cause of the condition e.g., treating a monilia infection, or treating with estrogen for estrogen deficiency in menopausal women or women with low estrogen from pituitary insufficiency, or drugs used for neuropathy e.g., amitriptyline or duloxetine, or gabapentin. Unfortunately, despite many treatment options, many women fail to gain sufficient improvement to allow enjoyable intercourse, or other pleasures related to clitoral stimulation or vaginal penetration. Presented here are anecdotal cases where the use of dopaminergic drugs, e.g., dextroamphetamine sulfate, has provided very credible evidence that this drug can markedly improve dyspareunia, vulvodynia, and other types of pelvic pain. The hypothesized mechanism of how this drug works is by correcting a permeability defect in the pelvic tissues which allows the infiltration of irritants into these tissues. The proposed mechanism of action of dextroamphetamine, which was the original intent of trying this drug to treat dyspareunia, is to release more dopamine from sympathetic nerve fibers. Dopamine diminishes cellular permeability. The cases recounted in this manuscript also show that other co-morbidities that are often associated with vulvodynia and pelvic pain are probably also related to increased cellular permeability, as evidenced from the observation that the symptoms of these co-morbidities also abate along with the amelioration of the dyspareunia.

Keywords: Dyspareunia, Endometriosis, Increased Cellular Permeability Syndrome, Dopaminergic Drugs, Vulvodynia

Definition and different types of dyspareunia

Dyspareunia in women refers to painful intercourse. The majority of the time dyspareunia pain occurs during intercourse; but sometimes the pain is delayed but does not actually occur during intercourse. Of course, sometimes some women experience both types.

Sometimes dyspareunia occurs with contact with the penis at the introitus and is related to pain initiating from the vulva or the vaginal entrance. Thus, it's sometimes referred to as superficial pain. For some women there is no pain with initial penetration, but only occurs with deep penetration, and is referred to as deep dyspareunia. Some women unfortunately experience both types.

There are some women who experience a constant discomfort in their vulvar region which is exacerbated by sexual intercourse. When pain is present constantly it is referred to as vulvodynia. Another term used is vulvovaginitis.

Vaginismus refers to difficulties in insertion of the penis or for that matter, even a finger, despite the apparent desire of a woman to have sexual intercourse or digital pleasure. Frequently vaginismus associated with dyspareunia is not related to inflammation but psychosocial factors. In the psychiatric literature, they refer to vaginismus that seems to be on a psychological basis as sexual pain/penetration disorder (SPPD) vs dyspareunia related to an inflammatory or hormonal, or structural issues e.g., genitourinary disorders with the specific name of genito pelvic pain/penetration disorder GPPPD [1-3]. This manuscript will be discussing dyspareunia related to a physical pathological entity excluding psychosocial causes.

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Etiology and Standard Therapy

Most common causes

Tayyeb and Gupta list the following etiologic factors that could cause dyspareunia: 1. structural, 2. inflammatory, 3. infiltration, 4. neoplastic, 5. traumatic, 6. hormonal, 7. psychosocial [4]. They list structural or anatomical causes as pelvic floor dysfunction, uterine retroversion, hymenal remnants, and pelvic organ prolapse [4]. Certainly, one may expect a good success rate in ameliorating dyspareunia by the surgical correction of an imperforate hymen or hymenal remnants. Uterine or urinary bladder prolapse can be treated with a pessary or surgery, but the dyspareunia is only sometimes fully corrected by the surgical procedure. It is far from certain that a uterine suspension can improve dyspareunia with a retroverted uterus, but hopefully this manuscript may generate some letters to the editor recounting personal experience of some gynecologists as to whether the uterine suspension procedure, or some other technique, improves dyspareunia from a retroverted uterus.

Pelvic floor dysfunction

Diagnosing pelvic floor muscle dysfunction is not as easy as detecting hymenal remnants as the cause of dyspareunia. First, the history should be consistent with the disorder, i.e., pain immediately with vaginal penetration or pain during intercourse as in other etiologies of dyspareunia. Sometimes with pelvic floor dysfunction, there may be also urinary dysfunction or dyschezia [5]. However, the main diagnosis rests on the physical exam which is determined by having the patients first try to contract the pelvic floor muscles followed by insertion of a lubricated finger into the introitus and then pressing on the pelvic floor [5]. If the physician or nurse practitioner elicits pain, then this is consistent with the diagnosis of pelvic floor dysfunction [5]. This, in my opinion, if pelvic floor physical therapy considerably improves the condition, then pelvic floor muscle dysfunction is likely the etiologic factor. However, if significant improvement does not occur, the dyspareunia is likely to be related to a different etiology.

Thus, before one proceeds with other expensive or invasive treatments e.g., local anesthetics or onabotulinumtoxinA or even using a posterior tibial, pudendal or sacral nerve stimulation one should consider an etiologic factor not mentioned by most reviews of the subject of dyspareunia and that is the increased cellular permeability disorder [6-9].

Vulvodynia

Chronic pain in the genital region that is present even without penile or digital insertion is considered vulvodynia. The pain may be generalized involving the labia majora, labia minora, clitoris, vaginal vestibule and introitus. Sometimes it may be localized and be restricted to one part of the vulva e.g., the vestibule and has been termed vulvar vestibulitis [10].

Interestingly, the pain, which is frequently described as burning, stabbing, or aching is not associated with pruritus [11]. When pruritus and pain is present one should look for an infectious cause e.g., yeast infection, and then treat with specific antifungal medications, or if trichomonas is present to treat with metronidazole. If pain persists despite treatment but no longer any evidence of infection by culture or vaginal cytology, one must consider a superimposed infectious vaginitis on top of pre-existing vulvodynia or the development of vulvodynia with infection as the initiating factor e.g., causing a permanent increased cellular permeability syndrome allowing unwanted irritants to infuse into vulvar tissue [8,9].

Vulvodynia is known to sometimes be associated with other pathological entities. It is not common to be present in women with chronic neurological disorders, and, in fact, treatment with levo-dopa for Parkinson's disease has been shown to cause marked amelioration of vulvodynia [12,13]. There is evidence of an association with other co-morbidities including interstitial cystitis, fibromyalgia, irritable bowel syndrome, and headaches [12,14]. Standard treatment options for vulvodynia overlap with treating pelvic floor muscle dysfunction to some degree because suggested therapies could include pelvic floor physical therapy, compounded or oral gabapentin, compounded or oral muscle relaxants, the tricyclic antidepressant amitriptyline or onabotulinumtoxinA [15,16]. Suggested therapies specific to vulvodynia but not dyspareunia from pelvic floor dysfunction, include wearing cotton underwear, washing clothes with mild soap and water, and avoidance of harsh detergents, perfumed toilet paper or vaginal deodorants and using 100% cotton menstrual pads with frequent changing for menses [17]. Other suggestions include topical anesthetics e.g., lidocaine 2% and cleansing the vulvar-peritoneal area with hygienic cleansing lotions e.g., BalnealR [17].

Sometimes post-menopausal women or younger women with estrogen deficiency from a gonadotropin deficiency, or premature ovarian failure, may have relative atrophy of the vulva and vagina and may have a constant burning pain or just pain with intercourse. This may be ameliorated by the use of vaginal lubricants before penile or digital insertion. If constant pain or dyspareunia persists then these other measures can be added to hormonal replacement,t and can be used in women with dyspareunia unrelated to estrogen deficiency, e.g., vaginal moisturizers applied several times per week [16]. Sometimes oral contraceptives may be the cause of vaginal dryness and improvement of dyspareunia may be achieved by discontinuing birth control pills and using an alternative means of contraception.

Interestingly, sometimes drugs that increase release of biogenic amines e.g., selective serotonin or norepinephrine reuptake inhibitors are used for treatment, but there is very little mention of using drugs that increase the release of another biogenic amine (and from this author's experience the most important biogenic amine) to ameliorate vulvodynia and/or dyspareunia and that is the biogenic amine dopamine. Relief is attained by dopamine diminishing cellular permeability and thus precluding infiltration of unwanted irritants into the introital tissues that may be the basic etiologic factor causing vulvodynia and/or dyspareunia [15,18-20].

The use of dopaminergic drugs to treat vulvodynia and/or dyspareunia

Author's Experience

In this author's experience, the various treatment modalities mentioned less commonly provide marked relief of introital pain upon penetration or continuous pain as in vulvodynia, but most frequently provide some, but inadequate, relief of symptoms, and sometimes no improvement at all. In contrast, the use of dopaminergic drugs e.g., dextroamphetamine sulfate (most commonly used), and cabergoline (less commonly used) provide quite satisfactory results for most patients.

The type of evidence that has the most credibility of a given therapy is a randomized controlled trial (RCT) with either a placebo or a comparison of the novel treatment to be considered vs the best of standardized treatments. Dyspareunia is not uncommon with some estimates of prevalence at 10-20%, and some suggesting 3-28% worldwide [21-23]. Thus, a generalized gynecological practice or a clinic dedicated to introital pain could organize an RCT to evaluate the efficacy of dopaminergic drugs for this type of genitourinary pain. Hopefully, this manuscript will generate interest in a medical practice that evaluates and treats a sizable population of women with the complaint of dyspareunia to initiate an RCT.

However, sometimes very convincing case reports may influence physicians to treat patients with a new therapy for a difficult problem, and hopefully these physicians will corroborate the efficacy of treatment and will publish their results or present their studies at medical conferences. These presentations or publications could be in the form of RCTs, larger series, or individual case reports. Thus, another way to promulgates knowledge and influence other clinicians to try dopaminergic drugs for dyspareunia and/or vulvodynia is to summarize some convincing case reports that have already been published.

Case report-vulvovaginitis in a pediatric patient [24].

A 6-year-old girl developed a malodorous vaginal discharge and constant vulvar pain. Despite multiple consultations with pediatric gynecologists and infectious disease specialists, they could not detect by culture or vaginal cytology an infectious etiology. She had also been evaluated by 2 pediatric endocrinologists to determine the etiology of her premature pubarche at age 7 and to see if there was some connection between the premature pubarche and the severe constant vulvar pain and malodorous vaginal discharge.

She had other associated problems. She had been a student with high academic achievement and was considered in the top 5% of her class. She started struggling academically and found it difficult to even pass academic tests. Another comorbidity was sudden considerable weight gain without evidence of changing eating habits. Related to her sudden academic change she sought the opinion of a pediatric neurologist, who did not have a presumptive diagnosis, and wanted to proceed with a spinal tap. Her mother, a nurse, was not in favor of a spinal tap, so at the age of 8 she consulted our reproductive endocrinology group to see if these symptoms could be related to the premature puberche.

Having a great deal of experience of successfully treating pelvic pain with the sympathomimetic amine and dopaminergic drug dextroamphetamine sulfate, we thought the weight gain was related to orthostatic edema another problem that responds to dopaminergic drugs [19,25-27]. Finally, we considered that her academic issues could be related to attention deficit hyperactivity disorder (ADHD) without hyperactivity, which we thought should also respond to dextroamphetamine [18-20].

We suggested that she re-consult the neurologist and see if that physician would prescribe dextroamphetamine. However, the neurologist believed that there was some more serious condition underlying her constellation of symptoms and insisted on performing the spinal tap. Furthermore, he was not in favor of treatment with amphetamines. Thus, we decided to treat her with dextroamphetamine sulfate 15mg extended relief capsules once per day starting at age 9. Her vulvar pain completely dissipated within one month, and with continued use her weight dropped to her previous normal weight. Also, she once again became a high academic achiever [24].

This case illustrates that vulvodynia can occur without being imitated by intercourse or acquiring infectious causes. Also based on the age that it occurred, we cannot imagine a psychosexual etiology. She denied any sexual abuse to a psychologist whom she had consulted prior to our initial visit. She is now 21 years of age and has not had any recurrence of the vulvar pain, but she continues on dextroamphetamine therapy.

Her menstruation did not begin until age 13. She has had little to no dysmenorrhea up to age 21. We diagnosed her premature puberty related to non-classic congenital adrenal hyperplasia (CAH) related to a 3 beta-hydroxy-steroid deficiency [28]. The CAH is probably unrelated to vulvodynia and is probably not associated with the increased cellular permeability syndrome.

A case showing that not only can dyspareunia be associated with other comorbidities, but they all respond to dopaminergic drugs [14].

A 34-year-old woman presented with a history since age 22 of dyspareunia with deep penetration. The dyspareunia was present the entire menstrual cycle, but it worsened premenstrually. Furthermore, it was getting worse with advancing age.

At the same time that her dyspareunia started, she also developed dysuria and urinary urgency. She also had nocturia waking her twice per night. In addition, she complained of ocular migraines which would start at the time of ovulation and get progressively worse throughout the luteal phase, then abruptly stop with the onset of menses. Within one week of taking dextroamphetamine extended-release capsules once per day beginning in the early luteal phase, all 3 pathological entities, i.e., dyspareunia, interstitial cystitis, and ocular migraines completely disappeared. She has been symptom free for 13 years staying on the same dosage [14].

This case supports the concept that relative increased cellular permeability may allow infiltration of irritants into various tissues leading to inflammation and pain in that given tissue. Thus, a dopaminergic drug correcting the relative dopamine deficiency in certain organ systems may provide great benefit in relieving pain in those organ systems as well as pelvic tissues.

Prior to publication involving dyspareunia and headaches associated with interstitial cystitis, we have published several other case reports showing the benefit of dopaminergic drug for treating refractory interstitial cystitis [29,30]. Similarly, we have published an interesting case of marked relief of ocular migraine headaches following treatment with dextroamphetamine that did not respond as predicted by ophthalmologists, that performing bilateral corneal implant surgery should relieve the ocular migraines which they thought were initiated by her keratoconus [31]. The patient with keratoconus did not have any pelvic pain nor did other patients whose treatment- resistant headaches responded quite well to treatment with dopaminergic drugs [32-

37]. Dopaminergic drugs have provided great amelioration of various treatment resistant conditions associated with or without pelvic pain or any pain for that matter [9].

Very severe dyspareunia and vaginismus associated with severe premenstrual rash [38]

A 32-year-old woman sought help for severe vulvodynia and vaginismus that prevented her from not only having sexual intercourse, but she could not even insert a tampon going back to menarche. She did not respond to psychotherapy, pelvic floor physical therapy, or amitriptyline. She did have dysmenorrhea also, but it was considered moderate, not severe. Her hymen was not imperforate, and the pain involved the vulva and introitus and vaginal vestibule as determined by touching with a cotton-tipped applicator.

She also complained that she had developed a painful facial rash for the past year usually starting 5-7 days before menses stopping abruptly with her menses. Dermatologists had diagnosed it as psoriasis.

She was started on 9.4mg dextroamphetamine immediate release tablets two times per day and at her 1-month evaluation she stated she was able to have penile penetration without pain (for 6 years prior penile penetration was not possible). She also inserted tampons without pain, and her moderate dysmenorrhea completely abated. Furthermore, she no longer had the premenstrual psoriasis rash. Her beneficial effect of dopaminergic drug therapy has persisted for 6 years. Her dyspareunia returns quickly the few times she could not fill her prescription because of drug shortage [38].

A case showing that dopaminergic drug therapy may be a much better option for severe dysmenorrhea and dyspareunia than surgery (unpublished case report)

A 33-year-old woman was referred by her father, a dermatologist, for severe dysmenorrhea that was refractory to oral contraceptives, norethindrone only, and letrozole (which she stopped shortly after taking it related to vasomotor symptoms and fibromyalgia). She had not been able to insert tampons and the few times she attempted intercourse; the pain was too severe to allow penile insertion. Her dysmenorrhea was so severe that about 8 months out of 12 she went to the emergency room for parenteral narcotics on her first day of menses.

She started on 9.4mg dextroamphetamine sulfate which was gradually increased to 18.8mg am and noon immediate release tablets (given as amphetamine salts 30mg twice a daily) and with this dosage her dysmenorrhea was minimal.

The almost complete resolution of the dysmenorrhea continued for 3 years. During this 3-year time period she never once had to visit the emergency room for parenteral narcotics. She did not even take non-steroidal anti-inflammatory drugs. She remained celibate because she did not have a boyfriend. Thus, she never tested whether the dyspareunia improved. However, interestingly, even a small speculation could not be inserted initially but after one year, she consented to have a pap smear, and a standard speculum was inserted without difficulty, and thus she had her first pap smear. She continued with sanitary pads just for personal preference.

Her menses had been regular, but after 3 years she was 3 weeks late for her menses, and when it came it was heavy with clots. For the first time in 3 years, she had dysmenorrhea of the intensity that was equal for the 3 or 4 months where a visit to the emergency room was not necessary.

She was a school teacher who was about to quit her job to write children's books. Her father consulted with our group and asked since related to her having dysmenorrhea with her last menses, should she have a laparoscopy before she loses the insurance? He and she were advised that probably the pain was related to the heavy menses with clots, and thus we advised that a laparoscopy would probably not be necessary.

Her father did an internet search, and he thought it may be best to do a laparoscopy to check for endometriosis just in case despite our opinion to the contrary. We explained to him the difference between laser vaporization vs excision technique for endometriosis and that we generally prefer the former. He decided that the excision technique seemed from his reading to be more effective and he arranged for a renowned endometriosis surgeon 800 miles away to perform the excision type of endometriosis surgery.

She was found to have minimal endometriosis and the small endometriotic implants were excised. This physician told her that she would not need to resume taking dextroamphetamine anymore. She did have 3 more menstrual periods without pain, but the 4th one was of such intensity that she needed to visit the emergency room again to be treated with parenteral narcotics.

Instead of informing our group about the return of pain (and we would have just restarted the dextroamphetamine), she called the endometriosis surgical specialist. He told her that he was suspicious that she had adenomyosis, and that only a hysterectomy would relieve the pain. She did not ask for our opinion but instead opted to proceed with a simple hysterectomy. The pathology showed no evidence of adenomyosis. Even if she was found to have adenomyosis, dextroamphetamine has been successful in providing marked pain relief even from this condition [39]. Her rationale was that she did not care if that hysterectomy would preclude her from bearing children in the future because without being able to have intercourse, she will never find a male partner. (She has not had intercourse during the treatment with dextroamphetamine but was able to have a speculum inserted without pain).

Three months after the hysterectomy, she began having severe dysuria, urgency and frequency. Urine cultures were negative. She was diagnosed with interstitial cystitis. She returned to our office, and we treated her once again with 18.8mg dextroamphetamine twice daily. Her interstitial cystitis because 95% improved. Surgical trauma or trauma without surgery can sometimes lead to increased cellular permeability causing some type of manifestation of the increased cellular permeability syndrome [9,40,41].

This woman after a period of time did find a male partner, while taking the dextroamphetamine, and she was able to have sexual intercourse with only mild discomfort. At times, because of drug

shortage, she was not able to take the dopaminergic drug, and the dyspareunia would return immediately. The symptoms of interstitial cystitis would not return unless she was not taking the drug for at least one month.

Conclusion

We have been treating various conditions in both women and men for over 45 years,
involving thousands of patients with dextroamphetamine, and no one has ever become addicted to the pharmacologic dosages that we use. Our first publication concerning its efficacy was published in 1984 involving dramatic improvement of very severe chronic urticaria [42].
There have been no deaths, no hospital admissions for serious complications, no subsequent evidence of long-term complications, no lawsuits, and no addiction. One can stop the drug abruptly without weaning, without any complications, or withdrawal symptoms, except for the possible return of the problem that was being treated.

Nevertheless, for some reason dextroamphetamine is considered a class II drug which places severe limits on its availability. At least in the United States a pharmacy can only dispense a limited amount based on a percentage of non-class II drugs that are prescribed which leads to a shortage of availability at times. Dextroamphetamine has provided marked improvement of severe Crohn's disease that had failed to respond to tumor necrosis inhibitors i.e.; adalimumab saving the patients from the suggested next step of treatment, i.e., a total colectomy [43]. Generally, dextroamphetamine sulfate would cost about $1000 per year vs adalimumab at a cost of a half million dollars! Tumor necrosis alpha inhibitors also carry the increased risk of future development of cancer or serious infections that can lead to death.

Somehow the concept has been generated to the public that amphetamines verge on being considered illicit drugs. The women with the vaginismus type of genito pelvic pain/ penetration disorders described in this manuscript was a physician. She stated that every time she filled her prescription the pharmacist would challenge her and make her feel like she was a drug addict or criminal [38].

Obviously, if there is a known etiologic factor causing dyspareunia i.e., fungal vaginitis or estrogen deficiency, that factor should be treated first, and only if not completely successful in eradicating the dyspareunia problem to then consider dopaminergic drugs. If a treating physician has found an effective treatment for a given patient e.g., psychotherapy or pelvic floor physical therapy, they should continue that treatment. However, if a specific therapy has not been completely successful, they may consider adding dopaminergic drugs, especially dextroamphetamine sulfate, though we have found some cases with very good response to the dopaminergic drug cabergoline, which has no narcotic restrictions. [37,44,45]. However, in general, it seems inferior in its efficacy compared to dextroamphetamine.

It is hoped that if this perspective influences other physicians to treat dyspareunia with dopaminergic drugs, they should submit case reports either corroborating or refuting the efficacy of dopaminergic drug therapy. Even more credible would be to influence an RCT or comparison trial for those physicians with a large population of patients with pelvic pain and dyspareunia. Case reports are important in that they show that a given therapy can work, but an RCT or even a larger clinical trial using previous treatment failures will influence more physicians to try this therapy. Even publishing convincing case reports from different treatment practices will certainly make the concept of increased cellular permeability with infusion of unwanted irritants leading to inflammation and thus dyspareunia and other forms of pelvic pain, more credible.

If corroboration of efficacy can be found, perhaps an organized large group of physicians can convince lawmakers to change or remove the class II label for dextroamphetamine. Hopefully corroboration of efficacy can influence pharmaceutical companies to develop even better dopaminergic drugs than dextroamphetamine to ameliorate dyspareunia, pelvic pain, and other medical conditions. Alternatively, they may develop other drugs that negate increased cellular permeability and thus preclude infiltration of irritants into tissues, that are not drugs that release more dopamine from sympathetic nerve fibers. Generating interests in scientists about the efficacy of amphetamines in correcting so many of these conditions could find that the drug works in some other manner than diminishing cellular permeability and thus may lead to the development of other drugs that can ameliorate these maladies. Our experience is that drugs that release more dopamine are more effective than some of the dopamine reuptake inhibitors used for ADD and ADHD, but a comparison study would be of interest. These types of drugs also have class II restrictions.

Limitations

1. Most of the data presented to support the efficacy of the treatment has been from anecdotal case reports. Very convincing case reports show that a novel therapy can be effective, but a larger series, whether placebo controlled or not or compared to another treatment modality is needed to ascertain what percentage of women with dyspareunia respond to dopaminergic therapy.
2. A larger study would also help to ascertain if there are certain types of dyspareunia that respond better to dopaminergic drugs. For example, does dopaminergic therapy work better when there is also associated dysmenorrhea? A study comparing efficacy of dextroamphetamine vs cabergoline in ameliorating dyspareunia or other types of pelvic pain would be interesting.
3. Efficacy of beneficial aspects of dopaminergic drugs for dyspareunia will be more credible if the same beneficial aspects can be corroborated by a different treatment center.

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