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New Insight into the Etiology and Treatment of the Vulvostomatodynia and Review of Treating Pelvic Pain with Dopaminergic Drugs

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ABSTRACT

Recently a review was published concerning studies on a seemingly odd combination of burning mouth and burning vagina termed vulvostomatodynia, when burning mouth co-exists with burning penis and scrotum. It is termed dysesthesia penoscrotodynia. A general term to include burning vagina and burning penis/scrotum is termed pelvodynia. One may think this could be a rare combination of two independent conditions that coincidentally happens in the same patient, but most physicians are not aware that there is probably one common etiology which is increased cellular permeability which allows infiltration into tissues of unwanted irritants. Thus, pelvic pain of various types may be associated with several other conditions including headaches, chronic fatigue, inflammatory bowel disease, and various skin disorders. For over 40 years, there have been published case reports showing marked improvement of various manifestations of this increased cellular permeability syndrome with the drug dextroamphetamine sulfate including vulvodynia even when standard therapies were unsuccessful. However, in a recent review of vulvosomatodynia and potential etiology and treatment the concept of increased cellular permeability of these mucosal tissues related to inadequate dopaminergic effect was not considered by that author the concept pf treating vulvodynia and stomatodynia with dextroamphetamine sulfate was related to its release of dopamine from sympathetic nerve fibers. Support for the concept that relative dopamine deficiency is probably the etiologic factor that was demonstrated by showing that a pure dopaminergic drug cabergoline, could also alleviate pelvic pain including vulvodynia. Furthermore, one publication, found 100% relief of vulvodynia following levo dopa treatment for Parkinson's disease, but more support for this theory is provided by the two new case reports described where one woman's dysmenorrhea and stomatodynia was eradicated by dextroamphetamine and another case where the stomadynia was markedly improved by dextroamphetamine but then later with cabergoline when dexamphetamine was stopped.

Keywords

Burning mouth syndrome, Dysmenorrhea, Increased cellular permeability syndrome, Sympathomimetic amines.

Introduction

There was a case described in 2002 of the burning mouth syndrome and vulvodynia coexisting in the same patient [1]. Another case was described in 2007, and the condition was termed vulvostomatodynia [2]. Subsequently stomatodynia was also found associated with a burning penis and scrotum, a term coined dysesthesia penoscrotodynia [3].

Some have combined dysesthetic peno/scroto-dynia and vulvodynia into one term called pelvodynia [1]. In fact, in 2022, there was a recent literature review on the burning mouth syndrome (BMS) and pelvodynia by Hamon et al. [4]. There are 2 types of BMS, primary and secondary. The former is idiopathic, whereas the latter has a known local or systemic cause [5]. This manuscript

will only refer to primary BMS. Recently, the International Headache Society has described BMS as "An intra-aural burning or dysesthetic sensation recurring daily for more than 2 hours per day for more than 3 months without evident causative lesions on clinical examination and investigation" [6]. BMS is not common with a prevalence of only 0.11% in the general population of the United States [7]. The prevalence is higher in people of advancing age and has been found to be present in 0.53% of women aged 70-79 [7-9].

A recent systematic review of the treatment for patients with BMS by Tan et al was published in 2022 [10]. They review the relative effectiveness of anticonvulsants e.g. clonazepam, gabapentin, pregabalin, antidepressants e.g. trazodone and citalopram, phytomedicines e.g. topical capsaicin, ultramicronised palmitoylethanolamide, herbal catuama, hypericum petrolatum, crocin, and lycopene enriched extra virgin oil, alpha lipoic acid by itself or in combination with gabapentin or vitamins, melatonin, low-level laser therapy, saliva substitutes e.g. topical lysozyme lactoperoxidase (biotene) or topical urea, transcranial magnetic stimulation, tongue protectors, and cognitive therapy. The authors concluded that no treatment achieves a 50% pain remission in BMS [10].

There are several different terms that have been used for vulvar or introital pain which include vulvodynia, vulvovaginitis, vaginismus, dyspareunia, or genito-pelvic pain/penetration disorder. There are many proposed therapies for vulvar and introital pain including avoiding vulvar irritants, wearing cotton underwear and pads, topical analgesics, estrogen, compounded or oral gabapentin, compounded muscle relaxants, amitriptyline, selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, pelvic floor physical therapy, cognitive behavior therapy, and surgical incision which have been summarized by Hill and Taylor [11]. Also, some suggest treatment with botulinum toxin A [12,13].

Whenever there is a large variety of treatments for a given condition, it generally translates that there was not one treatment that was very effective. Similar to BMS, for these vulvar and introital pain disorders, none of these treatments, in general, are very effective. One must distinguish short term vs long term clinical benefit for BMS. A complete spontaneous remission was observed in less than 5% of patients within five years after the onset of BMS, and less than half of the women with BMS had any significant improvement with treatment [14,15].

Two case reports will be presented in which two different seemingly unrelated medications were able to accomplish complete long-term remission of BMS. However, neither one of these medications were mentioned in the long list of medications typically used to treat BMS [4,10]. Though neither of these patients had vulvodynia associated with their BMS, reference will be made to published case reports where very long-term vulvodynia and other forms of long-term pelvic pain have been effectively ameliorated following treatment with these two drugs.

What the 2 drugs do have in common is that they both are dopaminergic drugs. One of the functions of dopamine is to diminish cellular permeability. These 2 case reports will help support a hypothesized mechanism as to the etiology of both BMS and pelvodynia that has not been proposed in the narrative review of Harmon et al., or other reviews of BMS,or for that matter, for the etiology of vulvodynia [4,5,10,11]. This aforementioned link between these 2 conditions occurring simultaneously in two seemingly unrelated parts of the body is the concept of increased cellular permeability of these 2 tissues, causing absorption of irritants into these tissues, which leads to inflammation and subsequent pain. Medications that increase the release of dopamine from sympathetic nerve fibers can correct the problem by diminishing cellular permeability and thus, eliminating absorption of irritants [16].

BMS is a rare disorder, though pelvodynia is more common. The main purpose of this manuscript is to make the readers familiar with dopaminergic drugs that effectively eradicated BMS, but would have most likely been effective if these patients also had the vulvar inflammation component. Thus, one of the main goals of this manuscript is to familiarize the readers, especially those treating gynecologic problems, but also those involved with dentistry and mouth disorders, with the common, but relatively unknown condition, termed the increased cellular permeability syndrome [16]. This condition can manifest with pain alone or with other problems in so many areas of the body, including, but not limited to, the mouth or pelvic tissues. An even more important goal of this manuscript is to demonstrate that very effective treatment does exist when using drugs that release more dopamine from sympathetic nerve fibers.

Case Reports

Case 1

The patient is presently a 49.5-year-old woman who initially sought our opinion to help her with recurrent miscarriage having lost her last 2 pregnancies in the 1st trimester. Since she was treated by our group for pregnancy number three with vaginal progesterone from early luteal phase through the 1st trimester until fetal viability was no longer seen, and the fetal products indicated a euploid fetus, in pregnancy four, we decided to treat her, in addition to supplemental P, with dextroamphetamine sulfate [17].

The reason for treating with dextroamphetamine sulfate was to inhibit the possibility of inadequate suppression of the normal increased cellular immune response accomplished by progesterone secretion, which suppresses the biological effect of dopamine, which, in turn, increases cellular permeability, leading to increased absorption of irritants, causing theoretically an increased cellular immune response. The normal increased cellular immune response, which is primarily an increase in natural killer (NK) cells, is hypothesized to create an autoimmune state to remodel some thick-walled uterine arteries to create thin-walled spiral arteries needed

for nutrient exchange between mother and fetus [17,18]. She was explained that experimental studies in our medical center suggest that the normal mechanism for preventing this normal increase in cellular immune cells in the fetal-placental microenvironment, from attacking the fetal semi-allograft, requires some mechanism to inhibit the cytotoxic action of these NK cells, macrophages and cytotoxic T cells. There is evidence that the protection normally provided to neutralize this increased cellular immune response is by the action of P in stimulating the increased secretion by embryonic cells, mesenchymal cells, and trophoblast cells of an immunomodulatory protein called the progesterone induced blocking factor (PIBF) [19-21].

The patient was advised that though frequently just adding supplemental P is sufficient to increase PIBF secretion to negate excessive cellular immune luteal phase activity, at times, it becomes necessary to dampen the cellular immune response further [22,23]. In her case, we thought that adding dextroamphetamine sulfate may help to prevent another miscarriage especially in view of her last miscarriage with a chromosomally normal fetus, plus the fact she also had P supplementation from early luteal phase until the time of fetal death [17].

In addition, this 36-year-old woman had other symptoms of the increased cellular permeability syndrome with mild dysmenorrhea, but severe, almost daily headaches, and constant mouth burning, especially involving her tongue, lips and palate. The headaches and BMS had been present for 8 years. She had previously consulted several neurologists, dentists, and oral surgeons, but the dentists and oral surgeons could not find any lesions or systemic illnesses to explain the BMS, so they diagnosed her with primary BMS. Neither the BMS nor the headaches were ameliorated with gabapentin or pregabalin.

She was treated with 15 mg amphetamine salts (9.4 mg dextroamphetamine sulfate) am and noon which completely eradicated her mild dysmenorrhea, and relieved both the headaches and the BMS by 50%. Raising the dosage to 30mg am and noon completely eradicated the BMS and headaches.

She conceived with vaginal P suppositories and 30 mg twice daily amphetamine salts. She delivered a full-term healthy baby. Normally, when we use amphetamines for conception, we stop this treatment after completion of the 1st trimester. The exception is when other symptoms are likely to return after stopping the dextroamphetamine sulfate. Based on past experience, we were confident that her headaches would remain much improved, even with the increased levels of estrogen during pregnancy, as long as she continued with dextroamphetamine sulfate [24-27]. However, this was the first case we had ever seen with BMS. Not only did the headaches remain completely abated during the pregnancy, but so did the BMS.

Because amphetamines do appear in the mother's milk, the woman wanted to stop the medication while nursing. Both her headaches and the BMS returned to full force within 1-week of stopping the amphetamines and continued for 5 months. Again, there was complete resolution of pain within 1 week when the amphetamine was restarted. She has remained on amphetamines for 13 years, and while taking the medication she hardly has headaches and, even when present, they are much milder. The BMS never returns while on medication. On occasion, she runs out of medication for a short time and headache and BMS symptoms will generally return.

Case 2

A 37-year-old woman consulted us hoping to find an endocrine cause of her failure to lose weight despite dieting. She was found to be mildly hypothyroid and was placed on thyroid hormone replacement. Her dosage gradually increased to 100 micrograms six days per week until reaching normal levels of serum free thyroxin and thyroid stimulating hormone. Her increasing weight gain ceased, but she was not happy that she was unable to lose weight.

Her history and physical examination were consistent with the increased weight being related to fluid retention. However, in the past she had been treated with diuretics which failed to help the edema or cause weight loss. Her condition was consistent with idiopathic orthostatic edema [28,29]. Originally George Thorn thought that dextroamphetamine sulfate helped edema by improving depression because he hypothesized that the etiology was psychogenic [28]. However, our own data, and research by David Streeten, suggested that the mechanism of action of dextroamphetamine was to release more dopamine, which, in turn, corrected a permeability defect of the capillaries which allowed transudation of intravascular fluid to extravascular spaces in response to the increase in hydrostatic pressure in the sitting or standing position [29-31].

We explained to the patient that idiopathic orthostatic edema is just one possible manifestation of the increased cellular permeability syndrome. She was thus asked questions as to whether she had any pain syndrome, and she mentioned that she has had primary BMS for 5 years. We advised her that we had treated one case of BMS where complete remission was attained by treating with dextroamphetamine sulfate. Thus, she decided to try dextroamphetamine. Unfortunately, she had tachycardia as a side effect of the amphetamine therapy and had to stop the medication. However, she had noticed significant improvement of her BMS when she was taking the dextroamphetamine sulfate. She asked if there was an alternative to dextroamphetamine sulfate. She was thus switched to another drug that releases dopamine from sympathetic nerve fibers, I.e., cabergoline. She noticed a mild reduction in her BMS after taking 0.25 mg cabergoline 2 x's per week. The BMS went into complete remission with 0.5 mg twice weekly, and the complete eradication of pain has persisted for 5 years.

Discussion

In the 2022 narrative review of BMS and pelvodynia, Hamon

et al. imply a connection between these 2 disorders related to a likely psychological etiology, or the influence of psychogenic factors possibly caused by the symptom in the continuance of the syndrome, even if the initial psychogenic factors are no longer present [4]. They state that, "In the case of vulvodynia, a psychosexual explanation could be that psychological or sexual abnormalities (vestibular or mucosal hypersensitivity or perineal muscle dysfunction) initially present with sensitization of the central nervous system, leads to allodynia and hyperalgesia. Women with chronic pain are cautious, attentive, pessimistic, and vulnerable in their intimate relationships. Therefore, catastrophism in these patients negatively affects their mechanisms of adaptation to pain. Thus, vulvodynia is influenced by both cognitive and affective factors." The argument is that these psychological factors may influence the oral cavity and the vulvar region more than other areas of the body because these tissues have a high concentration of sensory fibers [32].

In the review by Hamon of the treatment of BMS, psychotherapy and antidepressants are considered important therapeutic measures [4]. Dextroamphetamine sulfate is also considered an anti-depressant. Thus, those in favor of the aforementioned psychogenic etiology for these sensory disorders could argue the benefit of this amphetamine is its effect on the psyche [1,4,10]. This prompted the writing of this case report to promulgate the concept of the increased cellular permeability syndrome, at least in some cases of BMS and vulvodynia, because cabergoline is not known as an antidepressant. Case 2 achieved total remission of BMS (which rarely achieves full remission with other therapies) by treatment with cabergoline. This observation favors the concept of both dextroamphetamine and cabergoline having their beneficial effect through the release of dopamine, and thus diminishing cellular permeably, which, in turn, inhibits absorption into tissues of irritants, which may lead to inflammation and pain.

A case report was published concerning a 6-year-old girl who developed sudden severe pain in the vulva that was constant and quite debilitating. Her mother, a nurse, was emphatic that her daughter never experienced any previous sexual abuse. After consulting many physicians with different specialties including psychiatrists, neurologists, pediatricians and gynecologists, she sought the opinion of our reproductive endocrinology group. We suggested that she may find improvement of this idiopathic vulvovaginitis by treatment with dextroamphetamine sulfate. We were especially confident since she had some of the other manifestations of the increased cellular permeability syndrome including unexplained weight gain, and evidence of attention deficit hyperactivity syndrome (ADHD). Not only did her vulvodynia/vulvovaginitis completely dissipate after treatment with dextroamphetamine sulfate extended-release capsules, but so did her weight gain and her ADHD [33]. Thus, there may not be a unique condition of vulvostomatadynia, but merely vulvodynia associated with a much less common manifestation of the increased cellular permeability syndrome, i.e., BMS.

Another case of vulvodynia supports this concept. A 32-year-old woman consulted our reproductive endocrinology group for 2 reasons: 1) a very annoying desquamative facial rash that only occurred premenstrually and 2) to consult us about future fertility. Though she was planning to get married in 1 year, and not to have children until after the marriage, she stated that she was a virgin and not able to have intercourse with her fiancé during their five plus year relationship. In fact, she has never been able to insert a tampon since puberty related to severe introital pain. She had no relief of this problem despite psychotherapy, pelvic floor physical therapy, and amitriptyline. She was advised that some long-term skin disorders clear up very quickly following treatment with dextroamphetamine [34]. Sometimes skin disorders only manifest premenstrually because the breaking point of leakage of irritants into tissues does not occur until a further increase in cellular permeability occurs following the suppression of dopamine action by progesterone [35].

After 1 month of taking 9.4 mg dextroamphetamine sulfate am and noon she was not only able to insert a tampon painlessly, but she also had painless intercourse [36]. This quick response is not consistent with a psychogenic cause of her vulvodynia/dyspareunia, but consistent with the increased cellular permeability syndrome. It should be noted that she also had dysmenorrhea which was also abated [36].

Not only have there been other cases of premenstrual dyspareunia corrected by treatment with dextroamphetamine sulfate, but also simultaneously marked improvement of other manifestations of the increased cellular permeability syndrome e.g., associated migraine headaches and interstitial cystitis [37]. All types of pelvic pain may be ameliorated by dextroamphetamine sulfate e.g., chronic pelvic pain, dysmenorrhea, mittelschmerz, and even in one patient, in addition to pelvic pain, another manifestation of this syndrome, Crohn's disease [38].

Dextroamphetamine sulfate has been found to improve pelvic pain related to adenomyosis [39]. However, cabergoline has also been able to eradicate pelvic pain related to adenomyosis [40]. Cabergoline was also reported to relieve 10 years of severe dysmenorrhea, mittelschmerz, and 1 week of premenstrual pain in a 22-year-old woman [41]. Cabergoline was found to cause shrinkage of endometriosis better than LHRH agonists [42].

Recurrent aphthous stomatitis (RAS) could be considered a type of secondary BMS since in this case, severe oral pain is associated with ulcers, and frequently starts in childhood [43]. A 22-year-old woman sought medical relief for vasomotor symptoms, marked fatigue, and unexplained weight gain. After reading her medical history, it was discovered that she also suffered with severe RAS since age 3. The mouth pain was severe and would be associated with about 50 ulcers/day for at least 20 days a month without ever having any RAS free period for more than 2 weeks. All of her symptoms disappeared after treatment with 20 mg amphetamine sulfate extended-release capsules. Ten years later, her RAS is

still well controlled, but returns quickly if she runs out of her medication for short periods of time [44].

Interestingly, her brother, age 19, became a patient. He had RAS for about 25% of the year for seven years, but not as severe as his sister. However, he had extremely severe vasomotor instability. All of his symptoms abated with amphetamine treatment [44]. Dextroamphetamine sulfate has been shown, similar to the aforementioned young female who had normal ovarian egg reserve, to attenuate vasomotor flushing in other young women with normal egg reserve [45]. It has also proven to be effective for women with vasomotor symptoms with estrogen deficiency [46]. As mentioned, quite often the increased cellular permeability syndrome presents with multiple clinical symptoms. Sometimes pain is associated with another non-pain clinical condition e.g., women whose headaches and vasomotor symptoms markedly improved with dextroamphetamine treatment [47]. The chronic fatigue in the young women with RAS markedly improved with amphetamines. Improvement of chronic fatigues is another clinical benefit of treatment with dopaminergic drugs, and pelvic pain from endometriosis has been associated with a higher frequency of chronic fatigue syndrome [48-50].

Convincing anecdotal reports can provide useful information and lead clinicians to modify their present treatment methods. However, some clinicians, before adopting a new treatment strategy, want to see benefits documented in a larger series. Dextroamphetamine sulfate was found to be very effective in a study of 50 women suffering from chronic fatigue [49]. This drug was also found to be very effective for pelvic pain by Paul Carpentier in his patient population series [51].

The increased cellular permeability syndrome seems to be more prevalent in women. However, it can be seen in males who also seem to respond to dextroamphetamine sulfate treatment including some unusual conditions never reported in women e.g., mesenteric sclerosis and hereditary spastic paraplegia [52]. The etiology of this condition can be genetic e.g., brother and sister previously mentioned with RAS and vasomotor instability with the former being worse in the female and the latter worse in the male [44]. Another brother had an even milder form of RAS, but had a different manifestation, sever gastrocolic reflex [52]. Both symptoms were significantly ameliorated following dextroamphetamine sulfate treatment [52].

In the recent literature review by Hamon et al. concerning burning mouth syndrome and pelvodynia, they provide a table of the various treatments that have been published finding some beneficial effect on either BMS, vulvodynia, or penoscrotodynia. Though not otherwise referred to in their manuscript, but listed at the very bottom of the table, is a reference to a publication in 1996 by Ford et al. concerning oral and genital pain syndrome in men or women with Parkinson's disease [53]. Since Parkinson's disease is a condition associated with dopamine deficiency, if this theory of increased permeability related to relative dopamine deficiency is correct, one may expect an increase in pain syndromes and other manifestations of the increased cellular permeability syndrome in patients with Parkinson's disease. Interestingly, Ford et al. found a clinical improvement response in 20% of patients with BMS treated with levodopa, but also found 100% of women with vulvodynia to demonstrate improvement in their pain [53]. Levodopa is another dopaminergic drug, so the study by Ford et al. helps to support our contention that the association of BMS and pelvodynia is just another manifestation of the increased cellular permeability syndrome related to the need to diminish leakage of inflammatory substances into susceptible tissue [16]. The sensitivity of certain tissues may be genetic, but could require some other event e.g., infection or trauma to trigger it, or may be just related to tissue damage without genetic susceptibility as demonstrated in people with no previous history of symptoms of increased permeability syndrome where headache pain or severe stuttering result from concussions or brain surgery [52,54].

The original scientific interest for the lead author, Jerome Check, was cancer immunology. He first tried to make vaccines using autologous tumor cells treated in certain ways to make them more immunogenic [55-57]. However, he considered that because of similarities of the fetal-placental unit and malignant tumors (i.e., rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance) that if one could determine the fetal-placental mechanism of successful implantation, it would be likely that cancer would utilize a similar mechanism because the necessary factors would already be there. A model was created based on some research studies of how some of the factors needed for successful implantation with subsequent live delivery may require both the fetus and the cancer to evade immune surveillance, especially for the fetal-placental unit, because of the need to increase the presence of cellular immune cells in the fetal placental microenvironment for the purpose of converting some thick walled uterine arteries into thin walled spiral arteries [58-60]. Based on this model, it was hypothesized that some chronic illnesses could be related to relative dopamine deficiency from sympathetic fibers innervating that particular tissue. The first test case was a woman with a very severe chronic urticaria [61]. There were 3 choices of dopaminergic drugs at that time, levodopa, dextroamphetamine sulfate, or bromocriptine. We eliminated levodopa related to its side effect profile, but chose dextroamphetamine sulfate over bromocriptine because the latter drug was too new on the pharmaceutical market to rule out long-term side effects. Furthermore, we were not sure if the pituitary may be the only target for bromocriptine. Subsequently, we found that dextroamphetamine therapy provided marked improvement of chest pain in a woman with severe treatment resistant achalasia and then we kept searching for other refractory medical conditions that would be ameliorated from amphetamine therapy [62].

From the cancer standpoint, we did find that most cancers seem to utilize the same PIBF protein mentioned earlier [63]. The blocking of PIBF secretion by cancer cells using progesterone receptor antagonists has led to marked extension of a good quality of life in

patients with a variety of advanced metastatic cancer with no more conventional therapeutic options [59,60,64].

With over 40 years of very positive experience treating various medical disorders with dextroamphetamine sulfate, we have never had 1 patient become addicted to the drug, despite thousands treated over 40 years. Often patients run out of their medication due to shortages or we frequently stop it abruptly for pregnant women after the first trimester for women primarily taking it for dysmenorrhea and infertility or recurrent miscarriage, and yet we generally find an absence of withdrawal symptoms. Though young children take dextroamphetamine for ADHD, for some reason dextroamphetamine is considered a class II drug in the same category as fentanyl! Thus, many physicians are reluctant to try this medication, especially with the great emphasis today of avoiding class II drugs (especially opiates). However, as in case 2, we do find that cabergoline may also treat these recalcitrant conditions. However, our experience is that dextroamphetamine is more efficacious and has less side effects. Possibly the reason for better success with dextroamphetamine sulfate is that many patients can tolerate higher dosages if needed, whereas increasing the dosage of cabergoline frequently leads to intolerable side effects. One woman with very severe gastroparesis has had the problem totally corrected for 15 years but required 150 mg of amphetamine salts (equivalent to 95 mg of dextroamphetamine [65]. A recent case of severe chronic pancreatitis who had to pain relief from a combination of oxycodone, oxycontin, and fentanyl was able to stop these drugs and get almost complete pain relief from taking 90mg of dextroamphetamine [66]. Thus, since a recent review has been published concerning the association of burning mouth syndrome and vulvodynia, and the authors' (Hamon et al.) observation based on literature review that none of the many treatment options are very successful, we thought it was appropriate to present case reports showing extremely good improvement of BMS, with dextroamphetamine sulfate or cabergoline. Though neither of these patients had vulvodynia, we make the readers familiar with previously published case reports of dextroamphetamine markedly improving vulvodynia. Although, cabergoline has to our knowledge, never been tried for vulvodynia per se, we refer to a case where cabergoline did markedly improve severe premenstrual pain and dysmenorrhea [41]. Though one objective of this manuscript was to familiarize physicians and nurses involved with gynecology with the condition termed vulvostomatodynia, the main objective was to make the readers more aware of the increased cellular permeability syndrome, which commonly involves pelvic pain of various types, but may include other medical conditions that in most cases seem to respond to dopaminergic drugs. From the pharmaceutical end, hopefully, this manuscript will stimulate interest in developing even better dopamine releasing drugs for various autoimmune disorders that are frequently associated with pelvic pain e.g., inflammatory bowel disease, instead of drugs that by suppressing inflammation, also suppress the immune system leaving the patient more susceptible to eventually developing cancer or serious infections.

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