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REVIEW ARTICLE

Most Chronic Medical Conditions in Women are related to Increased Cellular Permeability and most can be Effectively Treated with Dopaminergic Drugs

Jerome H Check[1,2]*

[1]Cooper Medical School of Rowan University Camden, NJ, USA
[2]Cooper Institute for Reproductive Disorder, Mt Laurel, NJ, USA

Abstract

Based on a conglomeration of basic science research studies a model of hypothetical mechanisms of how the fetal semi-allograft can develop into a live baby was created. One of the tenets of the model is that it is necessary to remodel some of the typically thick-walled uterine arteries found during the proliferative phase into thin-walled spiral arteries to allow nutrient exchange between mother and fetus through an autoimmune mechanism during the luteal phase. The model suggests that the rise in progesterone inhibits dopamine. One function of dopamine is to diminish cellular permeability allowing irritants to infuse into the endometrium thus evoking an inflammatory reaction. The body must suppress these cellular immune cells from attacking the fetus. Progesterone activates membrane progesterone receptors which produces immunomodulatory proteins e.g., the Progesterone Induced Blocking Factor (PIBF), which negates the killing effect of cellular immunity. One hypothesis suggested that PIBF may be secreted by malignant tumors facilitating these tumors with foreign antigens to escape immunosurveillance and thus metastasize. Progesterone receptor antagonists e.g., mifepristone, which suppresses PIBF, have successfully increased length and quality of life in patients with a large variety of end stage treatment resistant cancers. Excessive permeability of various tissues was hypothesized to be related to possible relative deficiency of dopamine. A large variety of medical conditions have been ameliorated significantly by the use of dopaminergic drugs e.g. dextroamphetamine or cabergoline. The model explains why certain conditions may get worse premenstrually e.g., pelvic pain or headaches by the added suppressive effect of progesterone on dopamine. Though possibly further research may modify this model, based on the present hypothesis, a large number of treatment refractory conditions had very successful improvement based on treating with drug releasing dopamine thus correcting tissue permeability disorders.

Introduction

The title of this perspective is very provocative. It is the intention of this author to convince those reading this manuscript of the veracity of the

***Corresponding author(s)**

Jerome H Check, Cooper Medical School of Rowan University Camden, NJ, USA, 7447 Old York Road, Melrose Park, PA, 19027

Tel: +1-215-635-4156
Fax: +1-215-635-2304
Email: megan.oneil@ccivf.com

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title and thus hope that the readers will implement the treatment that will be discussed. This author feels confident that if any of the fellow physicians implementing dopaminergic therapy (the main dopaminergic drugs will be discussed in the text) that you will corroborate that this type of treatment will provide extremely efficacious solution to chronic health problems that are much more common in women but can also effect males. The author realizes that despite his publications in peer reviewed journals (mostly case reports) of the efficacy of this therapy in long-term chronic disorders that were refractory to standard treatment for over 40 years that this treatment remains obscure to most health care workers. Thus, this author apologizes that the large majority of the references refer to his team's published articles without providing studies from other researchers or clinicians because there are no other published studies that could be found to either corroborate or refute over findings.

Origin of the concept

Initially the main interest of the author was cancer research and more specifically cancer immunology. The author's initial research was aimed at trying to make weak foreign antigens on cancer cells more immunogenic to improve length and quality of life by autologous tumor vaccination [1-4].

The author was pleased by these initial studies but considered that the use of these techniques in humans would be time consuming and potentially very expensive (e.g., car-t therapy for human leukemia). Considering the similarity between the fetus and malignant tumors, i.e., rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance despite the fact that the fetus is actually a semi-allograft, the author decided to shift the emphasis of his research to try to determine how the fetus escapes immune surveillance with the hypothesis that cancer cells would borrow a similar mechanism already in existence for survival of the species to allow survival of the cancer [5].

Based on the author's research, but also many other studies from other researchers the authors hypothesized that a necessity for successful implantation requires an autoimmune attach by the cellular immune system directed against the thick walls of the uterine arteries that exist during the proliferative phase of the medical cycle to develop some thin walled spiral arteries whose thin walls are needed for nutrient exchange between mother and fetus [6,7]. To enhance an increase in cellular immune cells in the fetal placental microenvironment, the hypothetical model suggests that one of the functions of the biogenic amine dopamine is to decrease cellular permeability, and that the early secretion of Progesterone (P) by the corpus luteum blocks the effect of dopamine which allows infusion of irritants into pelvic tissues leads to the necessary increase in cellular immune cells (especially Natural Killer (NK) cells) needed for uterine artery cell wall remodeling [6,7].

Though embryo implantation is delayed 5 days to enable the development of spiral arteries by progesterone's role in creating mucin 1 which coats the endometrium for 5 days preventing attachment of the 3-day old embryo that reaches the uterine cavity. Subsequently it is necessary to now prevent these cellular immune cells (70% NK cells 20% macrophages, 10% cytotoxic T cells) from now attacking the fetal semi allograft [6,7]. Logic dictates that if secretion of P is needed to enhance an autoimmune attack of some designated thick-walled uterine arteries, one might assume that P would then have some additional physiological action to counteract these cells from causing immune rejection of the fetus.

The author's PhD was in reproductive biology and the thesis was entitled, "the role of progesterone in promoting embryo implantation and prevention of spontaneous abortion is through the stimulation of immunomodulatory proteins." One of these proteins that involves activation of membrane progesterone receptors is known as the Progesterone Induced Blocking Factor (PIBF) [8,9]. The hypothesis contends that the PIBF made by cells of the fetal-placental unit namely embryonic cells, mesenchymal cells, and trophoblast cells are responsible for the secretion of PIBF that is important for successful implantation and prevention of miscarriages [6,7,10]. This PIBF can be activated by various factors including, but not limited to, progesterone [7,10-12]. On the other hand, another cell circulating gamma/delta T cells in the blood, makes a slightly different PIBF that seems to require progesterone for stimulating membrane progesterone receptors to make circulating PIBF that seems to be important in preventing pre-term delivery [13,14].

Subsequently, PIBF was also found to be secreted by various types of cancer cells which may similarly inhibit cellular immune cells from attacking the malignant tumor and allow by local growth and

distant metastasis [15-18]. This hypothesis has been supported by the demonstration of marked palliative benefits and significant extension of lifespan in patients with a variety of very advanced end stage cancers with no other treatment options available, by treating with progesterone receptor modulators, e.g., mifepristone [19]. These cancers especially those devoid of the protective nuclear progesterone receptor include thymic epithelial cancer transitional cell carcinoma of the renal pelvis, malignant fibrous histiocytoma, leiomyosarcoma, colon cancer, pancreatic cancer, glioblastoma multiforme stage IV, fibroblastic osteosarcoma, small cell lung cancer, non-small cell lung cancer, urothelial cancer, and multifocal renal cell carcinoma [20-31].

Most physicians and scientists have been trained to pattern their choices of medical treatment based on Randomized Controlled Trials (RCTs). When there is a discrepancy with RCTs to then rely on meta-analyses. Case reports are generally given a low priority as to credibility.

Even if a given treatment proves to be effective in one given case, some of the concerns by the clinician/ scientist reading the case report may be that the treatment may not have ameliorated the condition but rather spontaneous remission, or that maybe this treatment can work as a rare case but the majority of other patients will not respond. Unfortunately, if one does not have financial backing, e.g., a pharmaceutical company to compensate clinicians to conduct an RCT, it is difficult to find clinicians willing to conduct such a trial. The author was approved by the United States Federal Drug Agency (FDA) for 2 principle investigators for a 40 patient investigation initiated study to evaluate the progesterone receptor modulator mifepristone for stage IV non-Small Cell Lung Cancer (nSCLC) that had advanced despite treatment with a minimum of 2 types of chemotherapy or immunotherapy but failed to find even one oncologist willing to be a principle investigator.

Thus, if one wants to share the knowledge of a way to treat end stage patients suffering from metastatic cancer with only a short, expected lifespan, one must publish these case reports but be sure that the ones chosen are convincing. In the aforementioned cases not only did oral daily mifepristone provide very quickly marked reduction in their suffering, but in many instances extended life by many years not just months. A large conglomeration of case reports may become more credible which sometimes will engender requests by journals to write an expert review [32,33]. The hope of the author is that not only will the publication of this review will convince more clinicians to try this therapy and thus extend the beneficial experts of this treatment to a much larger patient population but also lead to new ideas for other scientists to further improve efficacy of a given treatment which is this case is the use of progesterone

receptor modulators to treat not only advanced cancers but hopefully lead to its use earlier to further help the fight against this dreaded disease [34].

The topic from this special issue of the journal, "Women Health and Care." The fact that only women and not even secrete a significant amount of progesterone once they ovulate, the reader may get the mistaken impression that the use of progesterone receptor modulation for treating cancer is restricted to women with cancer. Indeed, the majority of cancers positive for the nuclear progesterone receptor are cancers seen only in women e.g., ovarian and endometrial cancer and certainly the large majority of breast cancer patients. However, the nuclear progesterone receptor may also be found in prostate cancer. However, as mentioned before the presence of nuclear progesterone receptor is protective and thus associated with a better prognosis. Mifepristone may suppress membrane progesterone receptor in overt immunomodulatory protein e.g., PIBF or another one called the progesterone receptor membrane component-1 protein, but this beneficial effect is somewhat neutralized by concomitant suppression of anti-cancer substances requiring the nuclear progesterone receptor [35]. Thus, probably the best time to start progesterone receptor antagonists with cancers positive for the nuclear progesterone receptor is when the cancer is metastasizing which is usually associated with the loss of the protective nuclear progesterone receptor [36].

Thus, in exploring ways to improve cancer immunology the author's research turned to finding the mechanism of successful embryo implantation and fetal survival. As mentioned, the model suggested that facilitation of methods to increase permeability of cells could lead to increasing infiltration of the endometrium with irritating substances evoking an increased cellular immune cell presence allowing the development of thin-walled spiral arteries [7].

This mechanism of increasing permeability allowing absorption of irritants to stimulate an increased cellular immune response may be present

in other tissues than pelvic tissues to allow the cellular immune system to attack pathogens which would be the irritants. This leads to the hypothesis that many autoimmune diseases may be related to an exaggeration of these normal physiological events causing pathological consequences. Increased inflammation may lead to pain, so it seemed likely that women with exaggeration of various types of pelvic pain in the pre- ovulatory time period or the luteal phase or during menses may be related to the person having borderline increased permeability issues in certain tissues including but not limited to the genio- urinary area with an increase in cellular permeability at this time.

In the rest of this manuscript there will be a discussion of the use of dopaminergic drugs for treatment of a large variety of medical conditions. Naturally, there are certain conditions that only occur in women e.g., dysmenorrhea, mittelschmerz, or vulvodynia.

The author presented this concept and model at grand rounds with preliminary data lending support to this hypothesis concerning how the fetus and cancer can escape immune surveillance and how the theoretical mechanism to promote inflammation may be involved in various inflammatory conditions when cellular permeability is exaggerated. One of the allergy specialists in attendance asked as to whether chronic urticaria may be related to unwanted infiltration of the skin with irritants related to permeability issues. This author agreed as to this possibility. The allergist referred a woman who was completely covered with chronic urticaria with hardly any hive-free days for 7 years. The question was what dopaminergic drug to use. At that time there were only 2 available on the United States pharmaceutical market, Levo-dopa and dextroamphetamine. Bromocriptine had not yet been approved as yet and was known as CB 154.

Dextroamphetamine sulfate was chosen over Levo-dopa because of a much greater safety profile. Within the first week all urticarial lesions completely disappeared. The allergist referred a second case with 3 years of chronic urticaria also resistant to standard treatments who also responded quite well. These 2 cases were published 40 years ago [37].

Interestingly, the first one of the cases never missed one day of dextroamphetamine for 25 years. Related to the drug shortage for one month, the drug was not available. She had no withdrawal symptoms or any suggestion of dependence. However, 3 days later she was covered with hives. They disappeared within 3 days of starting the dextroamphetamine a month later and has not had a single hive once again for another 15 years.

Though bromocriptine did become available for use through regular pharmacies, the results with dextroamphetamines were so good with very little side effects. So, this remained the predominant treatment over the last 40 years.

Dopaminergic drugs to treat medical conditions only found in women

Dextroamphetamine sulfate was found to be highly effective for various types of pelvic pain including chronic pelvic pain, mittelschmerz, dyspareunia, vulvovaginitis, dysmenorrhea, and vaginismus [38-42].

Dextroamphetamine has also been found to be very effective for pelvic pain of bladder origin i.e., interstitial cystitis [43,44]. Though interstitial cystitis is also present in men (though 1.5 x as likely in women) all the cases we have treated so far (with no failures) have been women success rates is marked improvement has occurred in 90% of the patients we have treated for this condition.

Though there have been many drugs to treat dysmenorrhea e.g., oral contraceptives or continuous progestins without estrogen of various types, impeded androgens, e.g., danazol or suppression of menses by Gonadotropins-Releasing Hormone (GNRH) antagonists (e.g., depo- leuprolide acetate) or GNRH antagonists e.g., elagolix. Dextroamphetamine is not only much more effective than these other medical therapies, as demonstrated by marked improvement in medical treatment failures, but has less side effects than most of them and is much less expensive than most of them [45].

However, one of the main advantages of using dopaminergic drugs, e.g., dextroamphetamine sulfate, as opposed to other medical therapies is that its use does not preclude the possibility of achieving a pregnancy while the treatment is being rendered. All other medical treatment either precludes achieving a pregnancy by either suppressing ovulation (oral contraception, depo-leuprolide acetate, elagolix), or causing an adverse endometrium for implantation e.g., low dosage norethindrone, medroxyprogesterone acetate, or danazol). Taking these drugs for several months then stopping to see that treatment could help a woman to achieve a pregnancy has been proposed

but there is no convincing evidence that this therapy improves fecundity [45]. In contrast there is evidence that dextroamphetamine can improve pregnancy rates, especially, but not limited, to women with pelvic pain related to suppressing excessive activity of the cellular immune system thus thwarting immune rejection of the fetal semi- allograft as related to chronic inflammation [7]. Dopaminergic therapy has been shown to help successful conception despite multiple previous miscarriages despite IVF with aggressive luteal phase support with progesterone [46].

One other advantage of dextroamphetamine over other medical therapies is that the chronic excessive inflammation state may hasten oocyte depletion leading to a greater frequency of Diminished Oocyte Reserve (DOR) in patients with a history of pelvic pain and/or endometriosis [47,48]. Thus, by stopping menses with these drugs egg depletion continues at the same rate whereas taking dopaminergic drugs may retard egg depletion by diminishing excessive cellular permeabilities this limiting infusion of inflammation irritants.

Though controversial even in 2024 as to whether surgical removal of endometriosis can improve fecundity or not our group favors that removal of endometriosis by laser vaporization or surgical removal improves fecundity [49]. Since sometimes surgical removal may diminish pelvic pain for at least a few menstrual cycles (sometimes, but less common, for long periods of time, and sometimes not at all). There is the possibility that endometriosis (which may be the result of increased tissue permeability allowing menstrual tissue to travel to ectopic places) may increase the tissue permeability allowing even greater infiltration of irritants into pelvic tissue and thus an even further increase in cellular immune inflammation with white blood cells, which, in turn, may increase the risk of these immune cells attacking the fetal semi-allograft.

Thus, the associated chronic endometrial state associated with pelvic pain with or without documented evidence of the presence of endometriotic implants, and the fact that endometriosis and/or pelvic pain is frequently associated with DOR, causes this author to favor dopaminergic drugs over laparoscopy. The reasoning behind this suggestion is that 1) inhibiting inflammation by diminishing excessive cellular permeability may be a more direct way to get to the root of the problem 2) the ameliorative effect of dopaminergic drugs are more long-lasting vs a potential very transient beneficial effect by removing endometriosis with surgery and 3) most of all the risks that surgery could further reduce egg reserve in women who may already have compromised enough reserve [7,50-53].

The dosage of dextroamphetamine sulfate is generally titrated to the dosage that will relieve the pain and other associated pathological entities if they are present with the assumption that the dosage that corrects the symptoms is probably the dosage needed to inhibit excessive inflammation.

If for some reason dextroamphetamine drugs cannot be used because of side effects, or other issues, one can treat with other dopaminergic drugs e.g., cabergoline [54]. Interestingly, one study found an increased frequency of vulvodynia in women with Parkinson's disease which according to this model of increased cellular permeability syndrome, the dopamine deficiency of Parkinson's should lead to some manifestation of increased infiltration of irritants related to lack of dopamine. Further supporting this concept, treatment with the dopaminergic drug Levo-dopa for the Parkinson's disease led to a 100% complete remission rate in the women with vulvodynia [55]. In general, however, our experience is that dextroamphetamine sulfate is more effective than cabergoline with less side effects Levo-dopa has too many side effects to use for treatment other than treating Parkinson's disease.

Both infertility and recurrent miscarriage can frequently be corrected by supplementing the luteal phase with extra vaginal progesterone to help increase PIBF secretion from cells of the fetal placental unit and circulating gamma delta T-cells. However, sometimes that is insufficient, and one must treat also with a dopaminergic drug to inhibit excessive cellular immune cells, especially NK cells [46].

Dopaminergic drugs to treat medical conditions that only occur premenstrually

With the secretion of progesterone in the luteal phase, cellular permeability is increased because of blocking dopamine, and as described, can increase pelvic pain premenstrually.

However, if there is borderline increased cellular permeability in other tissues the increase in serum progesterone may now increase the permeability of that given tissue above a critical level leading to infiltration of irritants with subsequent increased

inflammation and subsequently symptoms related to the inflammation of that tissue.

Thus, in some instances interstitial cystitis and migraine headaches may only occur in the luteal phase [39]. Dextroamphetamine has been shown to be beneficial for interstitial cystitis, migraine headaches and dyspareunia that only occurs in the luteal phase [39].

Dextroamphetamine also effectively eradicated premenstrual urticaria and anaphylaxis [56].

Dopaminergic drugs to treat medical conditions that are more common in women but also found in men

Many medical conditions fall under the category of autoimmune pathological conditions or idiopathic. These tend to be more common in women but may be seen in men also. In this section, the author will present conditions starting at top with the head and work down. In some instances, conditions may be insidious with an unknown etiology whereas others may also have a definite cause. References will be made to case reports about dopaminergic treatment, and in most instances the care will be one that was refractory to standard therapy but responded well to dopaminergic therapy.

There have been several reports of dopaminergic efficacy for insidious headaches [57,58]. Other times there may be a suspected etiology e.g., keratoconus, intra-cranial hypertension (pseudotumor cerebri) temporomandibular joint syndrome, or concussions [59-62]. In the case report on headaches following a concussion not only did the 2 teenagers get immediate relief from severe constant headaches and mental confusion despite months of no relief, but also immediately corrected severe post-traumatic stuttering [62]. Severe headaches resulting from head trauma relieved by dextroamphetamine sulfate has been reported in males as was severe headaches resulting from brain surgery [63].

The only case involving the eyes was an interesting case of correction of diplopia by dextroamphetamine that only occurred following orgasm [64]. Improvement of medical conditions related to the ears that improved with dopaminergic drugs have been reported for autoimmune hearing loss and Meniere's disease [65,66].

Dextroamphetamine has successfully eradicated very severe daily recurrent aphthous stomatitis of a 20-year duration in a young woman whose brother had the same condition [67]. It has also been found to be very effective for the burning mouth syndrome [55,68].

One of the strangest cases this author has ever seen was a 47-year-old woman who sought the author's advice on helping her with her problem of dysmenorrhea. Within the first five minutes of the interview in the middle of her talking she opened her mouth wide, and this huge fleshy ball popped out. Then after about five minutes it snapped back inside her mouth. She explained that this was rapidly relapsing and remitting angioedema of her tongue that has been happening for about three years since a tooth extraction. No one at any of the three well-known university medical centers had ever seen this problem before and none of the various treatments provided any benefit. Her dysmenorrhea completely disappeared with 30mg amphetamine salts but there was only mild improvement of the angioedema of the tongue. She was eventually switched to lisdexamfetamine dimesylate and with 130mg per day her angioedema of the tongue was reduced from 60-100 times a day as marked swelling of the tongue (which would cause significant breathing difficulties) to just 1-3 times per month [69].

We have treated several cases of chronic sinusitis and a couple cases of chronic thyroiditis but none of them seemed worthy of a case report. Similarly, we have treated mastalgia with dopaminergic drugs, but they have never been reported. Similarly, we have not published any case regarding the lungs or heart but interestingly a could patients who we were treating with amphetamines for some conditions subsequently developed atrial fibrillation. Their cardiologists appropriately advised them to stop the amphetamines, but interestingly the atrial fibrillation got worse, and the cardiologists advised them to go back on the amphetamine which seemed to reduce the episodes. Neither patient is actually taking medication for atrial fibrillation or had electro conversion.

Abdominal issues can occur with pain and/or diarrhea and/or constipation. One woman with abdominal pain of 25 years duration was almost completely ameliorated within one month of amphetamine treatment [70]. There was no association with menses [70]. One teenager had such severe constipation that in the last 6 years she never had a bowel movement any sooner than 9 days apart and frequently went 6-9 weeks without one. She has had one bowel movement for multiple years now as

long as she takes the amphetamine [71]. We recently published another case of severe constipation ameliorated by amphetamine, but the purpose was to show that one does not necessarily have to have pelvic pain to have uterine implantation defects but may be associated with other manifestations of the increased cellular permeability syndrome e.g., constipation. The woman with long term infertility with many expensive treatment failures quickly conceived after she started amphetamines [72].

Another case of amphetamines having tremendous ameliorative benefits was seen in a young woman who suddenly developed severe abdominal pain but also a 30-pound weight loss to 72 pounds. Monthly tests diagnosed her with pseudo intestinal obstruction. Not only did the pain dissipate but she quickly regained her weight with dextroamphetamine [73].

Amphetamines with their dopaminergic activity provided dramatic relief for 2 women with gastroparesis. One of the women seemed to over metabolize the amphetamine so that 150 mg amphetamine salts were needed to cause complete remission of the disorder which previously over 10 years caused her to be hospitalized 8-10 times per year with at least 1 week stays [74,75]. Interestingly a man with the problem also improved but had marked side effects of tachycardia and hypertension with standard dosages. It turned out that he did not metabolize the drug very well and he was controlled on 2.5mg amphetamine salts [63].

Dextroamphetamine has been reported to markedly improve inflammatory bowel disease even when they were not responding to corticosteroids or potent immunosuppressants e.g., adalimumab. What is impressive is that they all seem to respond so quickly including one woman who suffered with abdominal pain and 30 bowel movements per day for many years [77].

Another woman with a history of 8-12 very painful bowel movements per day with stage IV Crohn's disease, who failed to have significant improvement with all standard treatments including immunosuppression, was advised by a major university medical center that the next step was to have a partial colectomy of the most severely inflamed area, followed by double the dosage of adalimumab, then reconnect the bowel, and if symptoms recur do a total colectomy. Instead, she opted for dextroamphetamine and in a short period of time she was reduced to one painless bowel movement per day. The marked amelioration of pain and diarrhea lasted for several years [78].

What has not been reported was that she met a man at age 42 with whom she decided that she wanted to have a baby (she had never been pregnant before). We found that she had diminished oocyte reserve and a luteal phase defect, and she became pregnant with ethinyl estradiol to lengthen the follicular phase to develop adequate progesterone receptors and used supplemental vaginal progesterone in the luteal phase similar to another woman aged 45 who was successful with the same treatment [79]. Both conceived with natural intercourse.

After completing the 1st trimester, the 42-year-old woman with Crohn's disease was advised to continue the dextroamphetamine throughout the pregnancy for fear of a relapse. She was discharged to her obstetrician/gynecologist at the same university medical center in which the gastrointestinal division had been treating her Crohn's disease. They referred her to maternal- fetal medicine who advised her to stop the amphetamine because most autoimmune disorders will go into remission during pregnancy. She stopped the medication and within a few days she again was plagued with severe painful bowel movements. Maternal-fetal medicine referred her back to her gastroenterologist, who despite being informed of her previous excellent response to dextroamphetamine, recommended the partial colectomy with a diverting ileostomy. She had the surgery in the 2nd trimester. She did not re-consult our group for some strange reason to get our opinions. She delivered successfully and one-year post-partum with one year of adalimumab, she had a bowel re-anastomosis performed. Shortly thereafter her severe painful multiple bowel movements returned. She re-consulted us and has had very good correction of her Crohn's disease for 10 years until present. Unfortunately, in today's standard protocols all doctors in that practice must follow set protocols and thus, as seen in this case, doctors from a major university hospital that consistently voted as one of the 10 best hospitals in the United States, will subject a patient to their next standard treatment option even it has for more risks and much lower chance of being effective than a simple non-risky inexpensive treatment that was previously proven to be effective. One can understand a physician making the decision that they made unaware of previous case reports of a novel therapy not known to them. However, in this author's opinion it is unjustified to ignore a patient's

previous history demonstrating a great response to a treatment even if unknown by the consulting physician.

Dextroamphetamine sulfate has also been shown to be very effective for ulcerative colitis [80]. Recently we described another case of ulcerative colitis resistant to standard therapy but who had miraculous improvement with dextroamphetamine. However, the purpose of the report was to show that the use of this dopaminergic drug could concomitantly allow a successful pregnancy in a woman with long-term infertility not responding to "standard therapy" [81].

There have been some other interesting cases published concerning gastrointestinal issues, but they have been males. One young man had his gastro reflux problem resolved with amphetamines therapy [63]. Another tough longshoreman who had been healthy all his life suddenly developed such severe mid-e abdominal pain that he would fall to the floor writhing in pain, and he said he would cry like a baby. This occurred about 15 minutes after eating anything.

His condition defied diagnosis by multiple gastroenterologists. Finally, an extremely well-known medical clinic in the United Stated diagnosed him with a very rare condition (only 400 reported cases) called mesenteric sclerosis. They advised him that his mesenteric arteries were narrowed and when he eats the blood is diverted to his gastric arteries leading to bowel ischemia explaining his severe pain and his multiple episodes of vomiting per day. They also advised him that unfortunately there was no effective treatment and that from their experience, having seen more than 50% of the reported cases, he would be dead within the year from bowel perforation and sepsis. One month on dextroamphetamine sulfate he reported that he was capable of eating anything without pain or vomiting. He has been without symptoms for over ten years [63].

The only case of severe abdominal pain related to chronic pancreatitis that we have seen was in a gaunt man with severe abdominal pain and marked weight loss. The pain was very intense despite taking a combination of oxycodone, OxyContin, and fentanyl. After one year of OxyContin 90mg amphetamine salts he was completely off all narcotics, was basically pain free needing only occasional acetaminophen. He also regained 60% of the weight he had lost [82].

As far as the kidneys are concerned, the author has never treated a case of chronic glomerulonephritis or chronic pyelonephritis but based on the marked improvement of so many autoimmune and chronic inflammatory conditions this author suspects that these conditions would likely respond to dopaminergic therapy and possibly prevent or delay kidney damage and azotemia.

However, frequently chronic kidney disease leads to edema. By diminishing capillary permeability, dopaminergic drugs can help edema common in women unrelated to the menstrual cycle. This edema may result from leakage of intravascular fluid into the extravascular interstitial tissues related to the increase in hydrostatic pressure seen with the orthostatic position (sitting or standing) related to a delayed sympathetic nervous system response. This fluid retention may lead to not only edema but weight gain and generally is improved by treatment with sympathomimetic amines e.g., dextroamphetamine [69,83]. Dextroamphetamine sulfate proved to be much more effective for edema and weight gain than thiazide diuretics, spironolactone, or converting enzyme inhibitors [69,83].

The beneficial effect of dextroamphetamine sulfate for interstitial cystitis has already been discussed [39,43,84]. Dextroamphetamine sulfate was highly effective for a case of very severe urinary incontinence related to a neurogenic bladder [85].

As far as dermatologic conditions improving with dopaminergic drugs, some cases of urticaria have already been discussed [37,56]. Other interesting cases of urticaria responding very well to dextroamphetamine sulfate have also been published [86,87]. Over the years we have treated many cases of chronic treatment resistant urticaria and almost all cases have responded to dextroamphetamine sulfate.

Other types of skin disorders that have responded well to dopaminergic therapy include long standing eczema, discoid lupus erythematosus, bullous pemphigoid, and chronic pruritus without skin lesions [88-90].

Women may be more prone than men to problems with joints, ligaments, and muscles. Dextroamphetamine treatment has been found to ameliorate the pain of rheumatoid arthritis that was resistant to standard therapy and other associated problems, e.g., chronic fatigue [91].

Dopaminergic therapy has been very effective for persistent cases of severe fatigue attributed to Lyme disease or a result of chemotherapy [92,93]. One

young woman in her mid 30's had such severe fatigue that her husband had to carry her from room to room. She was diagnosed with autoimmune hepatitis. After one month of dextroamphetamine therapy, she resumed full time work as a nurse [94].

Other types of arthritic type pain relieved by dopaminergic drugs that has been reported includes fibromyalgia, frozen shoulder syndrome, and the aromatase induced arthralgia syndrome [95-97]. Though over the years we have treated many women with dopaminergic drugs for joint pain from osteoarthritis, none were so unique to be worthy of a case report. Long standing severe backaches and sciatica have responded very well to dextroamphetamine sulfate even in women who had no relief from surgery or have prevented them from undergoing surgery [98,99].

Medical problems related to the nervous system have responded very well to dextroamphetamine also. Headaches have already been discussed. One woman who was paralyzed from the waist down and confined to a wheelchair for 25 years with the Mitochondrial Encephalopathy Lactic Acid Stroke-Like Syndrome (MELAS) was able to walk after one month of treatment [100]. Over the years we have treated many women with multiple sclerosis and have noticed a significant reduction in the frequency episodes and improvement of fatigue. However, we have never reported any of the causes because of the nature of multiple sclerosis with long remission not unusual, we could not state for sure that dopaminergic therapy was responsible for the remission. However, one case was written that describes a woman with multiple sclerosis who was having rapid relapses upon initial presentation. She was wheelchair ridden. She did not have one more episode of multiple sclerosis in over 30 years with dextroamphetamine treatment. She moved to another state 1000 miles away, and because of the rules of prescribing class II drugs we could no longer write her prescription unless she returned to Pennsylvania to fill the prescription. She consulted a neurologist in her new state, and being unfamiliar with dextroamphetamine for multiple sclerosis, he refused to continue her therapy with that drug but placed her on ocrelizumab. She continued to be relapse-free. However, she did develop moderate fatigue. After 1 ½ years of this new therapy, she developed bullous pemphigoid which was very painful and long-lasting. The only therapy suggested by non-university dermatologists was tetracycline, but she did not show any response. She re-consulted our group and was placed back on dextroamphetamine, and the bullous pemphigoid lesions completely cleared in one week. For two years she has remained on ocrelizumab and dextroamphetamine and has not had any return of her skin lesions and her fatigue markedly improved (even before starting ocrelizumab) her paresis condition improved so that she was walking with the aid of a walker [101].

Though we have successfully treated several women with post-herpetic neuropathy with amphetamines, the one case that we published was an 89-year-old male who suffered for five years with very severe pain and requested medical suicide. He showed no improvement with anti-inflammatory medication, steroids, anti-neuropathy medication, and found little benefit to a combination of OxyContin, oxycodone and fentanyl. He completely responded to exclusive dextroamphetamine. Though he was pain free for five more years and died in his sleep from a myocardial infraction at age 94 [102]. Not only has the use of amphetamines enabled patients e.g., this 89-year-old man and the man with chronic pancreatitis to discontinue dangerous narcotics but one suffering from severe pain from multiple fractures from an improvised explosive device in the Gulf War in 1993 was able to stop high dosage narcotics in one month following amphetamine therapy [63].

Other neural disorders that have responded to amphetamines include hereditary spastic paraplegia and Parkinson's disease [63].

Discussion

A convincing case report informs a potential treating physician that a given therapy can work but there may be the exception rather than the rule. This author is making the statement that dopaminergic therapy works in the large majority of cases of these various disorders with few treatment failures. Those patients with side effect precluding the use of these drugs can be alternatively treated with bromocriptine or cabergoline, but in general, amphetamines are well tolerated, and usually are more effective, and with less side effects than bromocriptine or cabergoline.

Many physicians will only formulate their treatment plan for various conditions based only on Randomized Controlled Trials (RCTs). However, as frequently seen, one RCT has one conclusion, and another reaches opposite conclusion then one performs a meta-analysis reaching one conclusion only to be followed by another systematic reviewer reaching a different conclusion.

There is very little likelihood that a generic drug will generate interest in an RCT. Perhaps if an RCT is not feasible one can at least present the results as a large prospective study without controls. We only published one such study to date evaluating the effect of dextroamphetamine sulfate in improving the chronic fatigue syndrome. Fifty women were enrolled whose main complaint was severe fatigue. After six months from initiation of treatment, the fifty women filled out a questionnaire. The options were 1-symtoms worse, 2- symptoms status quo, 3- mild improvement, 4- moderate improvement, 5- marked improvement. The results showed that 48 women indicated marked improvement and 2 moderate improvement [103].

It behooves a physician when treating a patient with a given condition to choose not only the most effective treatment, but the one with the least side effects, the least potential long-term risks, and the one with the least expense. It is the author's opinion that dopaminergic drugs fulfill that requirement.

Hopefully this perspective will generate interest for other physicians to try this treatment for various conditions mentioned. If they find success, hopefully they will also publish case reports or case series or maybe RCT's comparing dopaminergic therapies versus the standard therapy of choice. However, if other treating physicians do not share this good experience, hopefully they will also report their findings.

Perhaps this perspective will stimulate scientists in different subspecialities to consider this experimental model, and with new information, refine it. Hopefully generating interest in more experimentation by other scientists may lead to even more efficacious treatment for many of these aforementioned conditions.

It is interesting that all these concepts were generated by research into determining the mechanisms used by the fetal semi-allograft to have proper implantation. Possibly this hypothetical model will stimulate not only new ideas to present death by cancer or improve suffering from non-malignant conditions but may lead clinicians or scientists to find better methods to treat infertility and thus bring in even more life.

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