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Editorial Article

Sympathomimetic amines are a safe, highly effective therapy for several female chronic disorders that do not respond well to conventional therapy

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Summary

Purpose: To evaluate the efficacy of sympathomimetic amine therapy for women with chronic disorders including, but not limited to, pelvic pain. *Materials and Methods:* Dextroamphetamine sulfate 15-mg extended release capsules were given to women with a variety of treatment refractory conditions including, but not limited to, pelvic pain. The dosage could be increased to 60 mg depending on tolerance to the medication and degree of improvement of the condition. *Results:* A very high percentage showed marked amelioration of their symptoms despite previous failure with medical or surgical therapy. *Conclusions:* The human species, especially women, seem to be more prone to certain specific tissue permeability defects and diminished sympathetic tone, which compounds the problem, since the sympathetic nervous system controls permeability. Thus, besides pelvic pain and interstitial cystitis, dextroamphetamine sulfate, which seems to restore sympathetic tone possibly by increasing dopamine secretion to the nerve fiber, provides gratifying relief to a variety of chronic disorders. These other disorders include: severe headaches, inflammatory bowel disease, gastrointestinal motility disorders, fibromyalgia, and other musculoskeletal pain, chronic fatigue syndrome, and urticaria.

Key words: Dextroamphetamine sulfate; Pelvic pain; Infertility disorders; Miscarriage; Pre-eclampsia; Ovarian hyperstimulation syndrome.

Introduction

As suggested by the title, it is my intent to convince the readers that the sympathomimetic amine, dextroamphetamine sulfate, is the most important single agent of all medications to help provide relief from suffering in women from a variety of medical conditions. It is my hope that if you are convinced as to the efficacy of this type of therapy by this "perspective", that this manuscript will have a major positive impact on your medical practice.

The reader should be forewarned that most of the evidence that will be provided will be from anecdotal case studies. There will be occasional data from a small series but only one randomized comparative study. However, I think you will agree that based on the dramatic quick response to treatment with dextroamphetamine sulfate in many chronic female-related disorders that previously failed to respond adequately to "conventional" therapy, that there is a high likelihood that this concept is correct and the therapy is quite beneficial.

One can hope that this study will generate interest for some group to initiate a large randomized controlled study. If such a study corroborates the benefits of dextroamphetamine sulfate in treating these disorders, this may convince a much larger body of physicians to try this therapy. However, with this drug available as a generic, and with the difficulty a pharmaceutical company would have in obtaining a unique patent for its use, since there are already many publications concerning its efficacy, it is unlikely a randomized controlled study will be performed since most are supported by pharmaceutical companies. Thus, realistically, my main goal is to share my knowledge with the readership to enable you to provide the same relief to your patients that I have provided to my patients for the past 30 years. Maybe, you will publish some unique case reports in various journals when you see how efficacious this therapy is or publish some case series of your own. Possibly you may write to the Editor of this journal if you have had positive experiences with this therapy but do not hesitate to publish any negative experiences. Credibility will be increased if confirmation of efficacy comes from a variety of different physicians.

At this point, you as the reader must be wondering what kind of female disorders respond to amphetamines. The discussion will emphasize pelvic pain but will not be limited

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to that subject [1-8]. The proposed mechanism is that certain tissues are more susceptible to permeability defects and absorption of chemicals and toxins into these tissue can lead to inflammation and pain [1, 2, 9]. If these noxious factors infiltrate mitochondria, weakness and organ malfunction may occur.

The sympathetic nervous system controls cellular permeability. The hypothesis leading to treating with dextroamphetamine sulfate is that hypofunction of the sympathetic nervous system related to diminished secretion of sympathomimetic amines, can be corrected by either the amphetamine substituting for the defective sympathomimetic amines or by the amphetamine stimulating dopamine [1, 2].

Chronic pelvic pain syndromes

Dysmenorrhea, deep dyspareunia, middleschmertz, chronic pelvic and chronic back pain

Endometriosis can be associated with pelvic pain syndromes including chronic pelvic pain, dysmenorrhea, dyspareunia, middleschmertz, or premenstrual backaches [10]. Yet, it is well known that some infertile women having no pelvic pain can be found to have extensive endometriosis. On the other hand, some women with excruciating pain are found to have mild or minimal endometriosis or no endometriosis at all [10].

Laparoscopic removal by laser has led to long-lasting relief of pelvic pain from endometriosis in a minority of cases. In most cases, the relief is short-lived or not at all [11]. Recurrence rates of endometriosis of 40-60% within one to two years has been reported [12]. Even laparoscopically lasering endometriotic implants combined with medical therapy do not prevent the return of pain from endometriosis [13]. Some argue that the reason why frequently the pain returns following laser vaporization is because there is the return of endometriosis as the laser does not completely remove the entire endometriotic lesion. Some claim that deeply infiltrating endometriosis is more associated with pelvic pain and this requires surgical excision rather than laparoscopic laser ablation [14]. There are studies claiming lower rates of recurrence of endometriosis with surgical excision in the range of 19-34% [15, 16].

One study by Yeung *et al.* provided results that were extremely interesting. They performed laparoscopies in teenage girls with severe dysmenorrhea and re-laparoscoped them two years later [17]. Not one showed a return of the endometriosis two years later when surgery was performed by careful excision rather than laser ablation [17]. However 50% had the return of pain [17]. I find this study extremely interesting. The study did claim that 50% showed relief of pain for two years, which may be higher than expected by laser vaporization [17]. However, 50% had return of pain without visual evidence of the return of endometriosis which suggests that the endometriosis, per se, is not the actual cause of the pain. A recent randomized controlled trial found no significant difference in overall visual analogue score for pain at 12 months when comparing excision *vs.* laparoscopic ablation of endometriosis [18].

Case reports have been described of relief of pelvic pain that was refractory to medical and surgical therapies that has responded to treatment with the sympathomimetic amine dextroamphetamine sulfate. We believe this works, by replacing or stimulating an increase in the defective neurotransmitter with subsequent restoration of normal sympathetic tone and therefore diminishing cellular permeability [2, 3].

One method of controlling pelvic pain, especially dysmenorrhea, is to use a low estrogen oral contraceptive or a low dosage progestin only, e.g., norethindrone 0.35mg, on a daily basis. The low dose estrogen can be used without a break to induce menses. If it works adequately, this therapy will fulfill the criteria of a treatment with low risk and relatively low cost. Unfortunately, the pain relief is not adequate in many women and further therapy is needed [4].

Suppressing estrogen levels by use of long acting gonadotropin releasing hormone agonists (GnRHa), e.g., depo-leuprolide acetate or the nasal inhalant nafarelin, has too many menopausal symptoms along with the possible risk of precipitating subsequent osteoporosis. Impeded androgens, e.g., danazol or ten-mg norethindrone acetate, have too many androgen side effects, e.g., weight gain, hirsutism, and acne and may cause atherosclerotic plaque [4, 19]. Since estrogen has been considered the main stimulator for endometriosis development, theoretically, it could be a target for therapy with aromatase inhibitors, e.g., letrozole. However, these agents were considered for treatment, but again too many menopausal side effects for a non-malignant non-life threatening disorders [19].

As mentioned in the aforementioned editorial, our preference for treating pelvic pain, by far, is the use of sympathomimetic amines specifically dextroamphetamine sulfate [4]. Since writing that editorial, we have completed a prospective series involving women with documented endometriosis with at least one year of severe pelvic pain not relieved adequately with oral contraceptives, surgery, or non-steroidal anti-inflammatory drugs (all three of these were a pre-requisite for inclusion). They could have also been treated with GnRHa's, but this was not a prerequisite for inclusion in the study. There were 15 women recruited. The average age was 32.5 years. These data were presented at the 2013 meeting of the American Society for Reproductive Medicine in Boston, MA [20]. The results are seen in Table 1. After three months, seven reported marked improvement (46.6%), five moderate, and three mild improvement. By six months, eight (53.3%) reported marked improvement, six (40%) moderate improvement, and one with mild improvement. Even the one with mild improvement said she did not want to consider a laparoscopy. Thus, 80% reported at least moderate im-

Table 1. — *Pelvic pain relief following treatment of 15 women with dextroamphetamine sulfate (dosage 15 to 30 mg extended release capsules) at three and six months.*

Months of therapy	Marked improvement	Moderate improvement	Mild improvement	No improvement
3	7 (46.6%)	5 (33.3%)	3 (20.0%)	0
6	8 (53.3%)	6 (40%)	1 (6.6%)	0

provement by three months and 93.3% by six months. The maximum dosage used in this study was only 30 mg extended release capsules.

The treatment with dextroamphetamine sulfate is so effective that one does not need to explore much further other treatment options. Dextroamphetamine sulfate is extremely well tolerated, is not addicting in the dosage used, and in our experience, it can be stopped suddenly without weaning and without any significant consequences, i.e., no withdrawal symptoms and no addiction. It can be mildly expensive if third party carriers will not pay for its off-label use. However, because of the stigmata of using a class-II drug that can be abused when used in very high dosages, there is a great likelihood that this drug will not demonstrate wide-spread use.

A definite benefit of dextroamphetamine sulfate is that it can be used to relieve pain while trying to conceive. No other therapy, other than surgery, will not prevent conception. It is safe to take during early pregnancy [21, 22]. It can even be used to help refractory infertility or to prevent miscarriage [23]. In a later section, another case report, though not reported as yet, will help support the contention that sympathomimetic amine therapy may help to reduce the risk of miscarriage and another case report will at least evoke the consideration that sympathetic hypofunction with increased cellular permeability may be the cause of unexplained fetal demise in the third trimester. Though surgery would not preclude attempting to become pregnant, there are data strongly suggesting that laparoscopic extirpation of endometriotic implants may compromise ovarian oocyte reserve [24-28].

With the positive pregnancy test the sympathomimetic amine can be stopped with little fear that the short time conceptus exposed to the drug could do harm, and as mentioned, most evidence suggests that this drug is safe to be continued by those women who need it for other reasons during the first trimester without the risk of congenital anomalies.

Case reports show that a treatment can be efficacious but does not give the reader the sense of how many failures one sees before finding a responder. A series, at least, provides a better concept of efficacy but does not eliminate placebo effect. However, a case report with dramatic results can sometimes be a more powerful tool to convince a reader to try a new treatment modality than even some controlled studies.

A previously unreported case provides extra credibility to support using amphetamines for pelvic pain while illustrating another point. A 35-year-old woman started out with dysmenorrhea at age 28 with a two- to three-day premenstrual component which gradually extended to continual pelvic pain, exacerbated by menses and severe dyspareunia so that intercourse was not possible. When she presented at age 35 for consideration of treatment for her pelvic pain, from her reading, she assumed we were going to try laparoscopic surgery. Instead we recommended dextroamphetamine sulfate. She had her doubts because besides the pelvic pain, she suffered from a severe anxiety problem. Unfortunately, despite a multitude of trials with anti-anxiety medication, she had side effects from them all, and thus was not on any anti-anxiety therapy. She was started on 15 mg amphetamine sulfate extended release capsules. Not only did she tolerate the medication, but it completely corrected the anxiety disorder. Even more important, except for mild dysmenorrhea, all the pelvic pain disappeared. Thus, even the presence of severe anxiety does not preclude amphetamine therapy. It was discovered that, at least in some cases, the drug can help treat anxiety.

Interstitial cystitis

We reported a small series on the use of dextroamphetamine sulfate for interstitial cystitis [6]. The small series required for entry that the subject was a woman with painful bladder for over a year who had failed to have adequate improvement from "standard therapies". The study required the triad of bladder pain, urgency, and frequency despite negative urine culture. Furthermore, cystoscopy findings had to be consistent with the diagnosis of interstitial cystitis [6]. Six cases were enlisted with four of the six having such severe symptoms that they could not function in daily society. Five of six women had nocturia also. Within one month of therapy on 15 mg dextroamphetamine extended release capsules, all six showed significant relief of dysuria, urgency, frequency, and nocturia. Five of six women increased the dosage of the amphetamine to 25 or 30 mg, whereas one had total relief at 15 mg and preferred no increase. Within two to six months the urinary symptoms were either completely gone or so mild as to be considered very tolerable [6]. The drug was continued for a year and at the end of the year the symptoms remained gone or nearly gone [6].

One unreported case illustrates the continuum between pelvic pain possibly "associated" with endometriosis and/or adenomyosis, and interstitial cystitis. A physician's daughter for several years had such severe dysmenorrhea that about eight/nine times per year she would go to the emergency room for parenteral narcotics to ease the pain. We placed her on amphetamine salts, which includes dextroamphetamine sulfate, and on 20 mg extended release capsules she had almost complete relief. This beneficial

effect persisted for several years from age 28-34. One cycle she had an anovulatory cycle and when menses ensued, she was passing large clots. For the first time she experienced fairly severe dysmenorrhea again.

She was assured that probably the pain was related to the clots, and with the control of her bleeding, her next menstrual cycle would not be painful. However, she was concerned that her insurance was about to be dropped, and if a laparoscopy was needed, she would have to pay out of her pocket. Her father strongly suggested a laparoscopy. Though a laparoscopy was not considered by our team, we were willing to perform it, if they desired. In our consultation, we discussed that we usually use laser vaporization and did discuss the surgical extirpation procedure for deep infiltrating lesions favored by some other gynecologists. Her father, a dermatologist, did a literature search and concluded that it would be best performed by a surgeon using the non-laser technique. His computer investigation concluded that the best surgeon for his daughter was in a city 965 km away with a world renowned endometriosis surgeon skilled in removing deep infiltrating endometriotic implants.

She only had stage I endometriosis with only a couple small implants, which were removed. The surgeon advised her that now with the endometriosis removed she can stop the amphetamine. She complied. She had no dysmenorrhea for three months, but on the fourth month it was as severe as ever, requiring a trip to the emergency room. She called the surgeon and he explained that she most likely has adenomyosis and that the only treatment would be hysterectomy. She did not ask our opinion, but proceeded with simple hysterectomy. Within a few months she developed classic symptoms of interstitial cystitis. She came back to our office and she was retreated with dextroamphetamine sulfate and her bladder symptoms completely disappeared. If this single woman marries and wants a child, she will need an extremely expensive gestational carrier. This case is an example of why sympathomimetic amine therapy should be chosen before any surgical procedure [4, 11]. It is interesting that without a uterus, the permeability defect shifted to the urinary bladder. She never had symptoms of interstitial cystitis before. The case supports the concept that endometriosis may be associated with the sympathetic neural hyperalgesia syndrome causing severe pelvic pain, but not the actual cause of it, since the removal of her one endometrial implant by one of the world's leading endometriosis surgeons failed to improve her pain, whereas amphetamine did relieve the pain. Furthermore, the surgeon's presumptive reason for failure was that the pain was probably from adenomyosis (explained the lack of success of laparoscopic excision). However, the pathology report on the uterus removed by hysterectomy showed no evidence of adenomyosis. Finally, it was extremely interesting that without a uterus the syndrome shifted to her bladder, and thus illustrates a similar mechanism for dysmenorrhea and pelvic pain of bladder origin [5, 6].

Other pelvic pain syndromes – vulvovaginitis, backache

One interesting case report involved a six-year-old girl with premature pubarche who developed a severe chronic vulvovaginitis that responded completely and very quickly to treatment with dextroamphetamine sulfate [8]. Most of the multiple pediatric endocrinologists and pediatric gynecologists that she consulted focused on some occult connection to her three hydroxysteroid dehydrogenase type of congenital adrenal hyperplasia playing an etiologic role when the problem was related to increased permeability of the vulva related to sympathetic hypofunction [8].

Another woman with severe backaches that were attributed to herniated disks wanted to avoid orthopedic surgery. She showed dramatic improvement with dextroamphetamine therapy and the pain has been eradicated for years while on therapy [7]. Her dysmenorrhea that had been present long before the backache actually started, also dissipated [7].

Prevention of miscarriage

There is still controversy as to what treatments are beneficial for the prevention of recurrent miscarriage. I am a strong proponent of progesterone therapy [29-33]. What therapies are available for women who continue to have first trimester pregnancy losses despite progesterone therapy?

We considered that a miscarriage could possibly be related to inability to preclude chemicals and toxic factors from invading the placenta related to sympathetic nervous system hypofunction. Indeed, two cases were reported suggesting that successful completion of the first trimester could have been aided by sympathomimetic amine therapy [23]. One case related to severe oligoasthenozoospermia in her male partner had in vitro fertilization-embryo transfer (IVF-ET) at another reproductive center and conceived three times, but despite progesterone supplementation, had three first trimester miscarriages. She also conceived three more times with donor sperm insemination and progesterone support. However, all three ended in first trimester miscarriages. This 36.8-year-old woman successfully delivered a live baby full-term with her first IVF-ET cycle in our practice by also treating her with dextroamphetamine sulfate 15 mg extended release capsules [23].

Another woman conceived two times with IVF-ET and one frozen ET and miscarried all three, including a documented normal male fetus. She was successful in cycle 4 with the addition of dextroamphetamine sulfate [23].

Another unreported woman in her mid-thirties had primary recurrent miscarriages three times in natural cycles. I was very optimistic that as long as her follicle was ma-

ture (which our testing concluded was mature) that taking progesterone supplementation in the luteal phase and throughout the first trimester would be all that was needed for a successful outcome. She conceived quickly, but despite aggressive progesterone supplementation, she had miscarriage number four. A gestational sac was evident but no fetal pole, so chromosome analysis on the products of conception was not performed. A fifth pregnancy also resulted in miscarriage and chromosome analysis showed a normal female. A sixth and seventh miscarriage found normal male fetuses. We discussed the possibility of treatment with dextroamphetamine sulfate. We had her talk with one of our employees who had failure to conceive at another reproductive center at age 35 despite several cycles of IVF-ET and many cycles of intrauterine insemination. Though we were successful with IVF-ET in achieving pregnancies in all three IVF-ET cycles (40 years old for cycle 1), she miscarried all 3. She was however, successful with her fourth cycle with the addition of amphetamine and completed her second trimester. Unfortunately our employee developed pre-eclampsia and had neo-natal death of a premature baby. Meanwhile, the primary aborter with seven first-trimester miscarriages on our advice, and after talking to our employee when she was late in the second trimester, decided to take the dextroamphetamine sulfate 15 mg extended release capsule. She delivered a full-term healthy baby. Subsequent to this, our employee now 42 years of age decided to try IVF again. Two weeks before her expected start date for her stimulation drugs, she visited her hair dresser. She remembered that her head had been yanked back fairly hard when she was having her hair washed. Four days later, she had a stroke. It was found to be secondary to emboli from a dissected right carotid artery which may have occurred during the hair-washing. We were now faced with a dilemma. Though she had 99% recovery, we believed that she could be at more risk from emboli during the hypercoaguable pregnancy state. The safest solution would be the use of a gestational carrier. However, my employee could not afford one. The primary aborter who had seven losses in a row before using dextroamphetamine sulfate offered to be a free gestational carrier. Only two embryos were transferred but both implanted. The gestational carrier stayed on the dextroamphetamine sulfate until the full-term delivery of twins (this is the first report of these two cases).

The possibility exists that absorption of unwanted chemicals or toxic material into the placenta can cause unexplained fetal demise, even in the last trimester [34]. A woman in her early 30's had a stillbirth at 31 weeks, yet pathological evaluation found no fetal or placental abnormalities. The final diagnosis was chorionic villitis. In another pregnancy, at 31 weeks, she did not detect movement, and this was confirmed by ultrasound, though cardiac activity was present. An emergency cesarean section was performed. Though there was marked fetal acidosis, the baby girl responded quickly once outside the womb and everything eventually turned out fine [34].

The woman had severe debilitating arthritis in the hands, elbows, and knees which failed to respond to non-steroidal anti-inflammatory drugs, methotrexate, prednisone, and adalimumab. She was offered dextroamphetamine sulfate and this was the only agent that provided relief [34].

She wanted to have another baby (this part is unreported). We considered that the same condition causing the joint pain, which we assumed was related to absorption of toxic material into the tissues related to sympathetic hypofunction and therefore increased cellular permeability, could be the etiologic factor causing the last trimester issues. The only other option was to consider IVF with transfer to a gestational carrier. The latter option was cost prohibitive, so they were going to try another natural attempt, only this time just continue the sympathomimetic amines which were markedly helping her arthritis. However, her husband, a lawyer, made full partner. They thus believed they could afford the $80,000 gestational carrier fee. She conceived and at 32 weeks the gestational carrier had premature rupture of membranes. The insurance for the gestational carrier did not fully cover the hospital visit. The baby cost about $250,000.00 out of pocked for this couple.

Another woman failed to conceive despite several IVF cycles but was able to conceive the only two times she took dextroamphetamine sulfate [35]. Though one can argue that the conception may have merely been fortuitous, one cannot deny that the drug markedly relieved chronic complex regional pain syndrome (reflex sympathetic dystrophy), making the argument more credible that it helped implantation also [35]. All other therapies had failed to help her severe wrist pain.

Other disorders specific to women

Vasomotor symptoms

The first case report of improvement of vasomotor flushing by dextroamphetamine sulfate was in a 29-year-old normal estrogenic woman with no evidence of diminished oocyte reserve [36]. She described typical flushing and night sweats. Her day 3 serum FSH was only four mIU/mL. She was 99% improved within two weeks of taking dextroamphetamine sulfate 20 mg daily. She had failed to improve with oral contraceptives [36].

The benefits of sympathomimetic amine therapy for vasomotor symptoms extend to women with estrogen deficiency and perimenopausal women also [37, 38]. The sympathetic nervous system controls the temperature regulation system of the hypothalamus. It is not clear if this problem is related to simply low sympathetic tone as a direct effect on the temperature regulation system, or do chemicals infiltrate this area of the brain related to increased cellular permeability and cause the vasomotor instability?

Post-partum depression

One suspected cause of post-partum depression is estrogen deficiency related to a delay in restoring the hypothalamic pituitary ovarian axis related to suppression of LH and FSH from prolonged sex steroid exposure during pregnancy, compounded by persistent high prolactin levels [39]. Indeed, estrogen therapy had helped relieve post-partum depression in some women [40, 41]. Some believe that estrogen followed by progesterone supplementation is more effective than estrogen alone [42].

Pregnant women may be more prone to transient hyperthyroidism with lymphocytic thyroiditis [43, 44]. Because the gland is injured, in the post-partum period, transient hypothyroidism may occur until the injured thyroid can heal and start making thyroid hormone again [45, 46]. Thyroid hormone replacement has been found to help depression in some cases [43-45]. Because the post-partum period may be associated with lowering of certain biogenic amines, e.g., momamine oxidases and serotonin, anti-depressants are frequently prescribed, especially the newer serotonin re-uptake inhibitors and bupropion [46].

Another unreported case will provide an example once again of a woman failing to gain relief from standard therapy, yet quickly responding to dextroamphetamine sulfate. A woman at age 33 developed post-partum unipolar depression shortly after the successful birth of twins. The depression was so severe one month after delivery that she was committed for hospitalization. The hospitalization did not result in much improvement. She had received both psychosocial treatment and psychotherapy and was started on antidepressant medication.

Though she was discharged from the hospital on fluoxetine Hcl and bupropion, she was still so depressed that she could not return to work. She was also taking topiramate for migraine headaches, but this drug provided her no relief. She had resumed regular spontaneous menses, so there was no evidence of estrogen deficiency. Her free thyroxin levels and thyroid stimulating hormone levels were obtained and they were normal. She was started on dextroamphetamine sulfate extended release capsule 20 mg once daily. When she returned in one month, she stated that within one week her depression completely lifted, her fatigue markedly improved, and she had not had a migraine headache all month. Her insomnia also dissipated.

Other medical conditions more prevalent but not restricted to women

Inflammatory bowel disease

Women seem to be more prone to autoimmune disorders which include inflammatory bowel disease. A 39-year-old woman with Crohn's disease Stage IV of 12 years duration had failed to respond to mesalamine, prednisone, cyclophosphamide, inflixamab, and adalimumab. Colonoscopy showed involvement of the entire colon [47]. She was advised to have a partial colectomy and diverting ileostomy. Instead, she tried dextroamphetamine sulfate 20 mg per day and was 90% improved in one week and 100% improved by one month (eight to 12 very painful bowel movement per day reduced to one painless bowel movement). A repeat colonoscopy found no evidence of Crohn's disease [47].

Subsequent to that publication, the woman had remained in clinical remission for three years. She sought help to get pregnant at age 42. She was found to have diminished oocyte reserve as evidenced by elevated day 3 serum FSH and a short follicular phase. She was treated with ethinyl estradiol to lower FSH and lengthen the follicular phase and luteal phase support with supplemental progesterone similar to the technique that we successfully used for a 45-year-old woman with a similar problem [48]. She conceived on her second treatment cycle. She was discharged after completing the first trimester, and she was advised to continue with the amphetamine salts that she had taken during the first trimester until delivery. She was also advised to continue with progesterone until at least 36 weeks. Her obstetrician referred her to a maternal-fetal medicine specialist at a major university hospital. She was told to stop the amphetamine because they were not aware of its use for Crohn's disease (they made no effort to contact our office for an explanation). They advised her that most of these autoimmune disorders go into remission anyhow during pregnancy. They also stopped the progesterone because this was her first pregnancy and they usually only prescribe it beyond the first trimester for those with previous pre-term delivery.

During her second trimester, her Crohn's disease severely flared up. The gastrointestinal team at this university hospital was consulted and they strongly suggested partial bowel resection and diverting ileostomy. This procedure was performed. She delivered at 32 weeks but the baby survived and is doing well. Following the delivery, her bowel was re-connected. Shortly after surgery, her frequent bowel movements with severe dyschezia returned. The gastrointestinal specialist recommended total colectomy and permanent ileostomy. Instead, she returned to our office and she was re-started on the amphetamine salts. Her symptoms quickly abated again and she has been well controlled now for 1.5 years post-partum on dextroamphetamine sulfate.

Another unreported case of Crohn's disease is very interesting. A 41-year-old nurse married to a specialist in internal medicine had a 25-year history of Crohn's disease and had failed to respond to any of the standard medications used for Crohn's disease, similar to the other case just previously mentioned, and also failed to improve following two partial bowel resections. She finally had a total colectomy and a permanent ileostomy. Unfortunately, her abdominal pain was still so severe she needed to take hydromorphone hydrochloride every two to four hours.

She decided to try to have her first baby. She went to a reproductive endocrinologist at a major university medical

center who advised her that because of her age and diminished oocyte reserve, as evidenced by an elevation in day 3 serum FSH, that she would require donor oocytes with the embryos transferred to a gestational carrier because of her need to take such a high dosage of hydromorphone with the highly likely addiction of the baby. She agreed to the gestational carrier but wanted to try IVF with her own oocytes. She failed to achieve a pregnancy twice despite transfer of embryos to gestational carrier. The reproductive endocrinologist refused to try again with her own oocytes insisting on donor oocytes.

The woman sought a second opinion still wanting to use her own oocytes and consulted our clinic. We explained that the higher FSH regimen used by the other IVF center would likely create chromosomally abnormal embryos related to meiosis II errors [49]. A better chance of success would be achieved by mild FSH stimulation [50]. We also advised her that it may be possible to improve the pain using a safe drug in pregnancy, dextroamphetamine sulfate, and eliminate the hydromorphone hydrochloride. Within one month, her pain was completely eradicated. She conceived on her first embryo transfer to her own uterus with her own oocytes and delivered a healthy baby. For three years she has remained pain free just taking dextroamphetamine sulfate.

Another woman (unreported case) had right lower quadrant pain for 22 years. The pain was unexplained but hypothetical causes that were entertained included chronic appendicitis, chronic salpingitis (though laparoscopy showed normal fallopian tubes), and pelvic congestion syndrome. Her daughter was a patient taking dextroamphetamine sulfate for pelvic pain and edema. The mother requested to try the drug to help her edema and weight increase despite dieting. She never dreamed that the treatment would eliminate the constant daily right lower quadrant pain of 22 years duration within one month of treatment. In fact she had never even mentioned it during her initial consult when we took her medical history. She never thought that anything would relieve the discomfort.

I chose two inflammatory bowel cases with pregnancy implications. Space limitation does not allow any in depth presentation of other cases with gastrointestinal issues where there was chronic severe symptoms refractory to standard therapy but who responded dramatically to amphetamine therapy. These included other types of inflammatory bowel disease, e.g., ulcerative colitis [51], lymphocytic colitis (accepted for publication but not in press yet), and gastrointestinal motility disorders including achalasia [52], gastroparesis [53], pseudointestinal obstruction [54], and pathological constipation [55].

Severe headaches

Women seem to be more prone to headaches than men. We have published unique case reports of women suffering from long term headaches not relieved by conventional treatment that responded very well to amphetamines [56, 57]. Dextroamphetamine sulfate completely abrogated severe headaches related to intracranial hypertension that failed to respond to acetazolamide [58]. The papilledema completely disappeared [58]. Which reminds me of a woman with 25 years of migraine headaches which a neurologist told her 25 years before was probably the start of multiple sclerosis (unreported case). However, after 25 years, there was no evidence of multiple sclerosis. A friend of hers came to our office and her long-term history of migraines was corrected. Thus, this woman came to our office to try this therapy. It completely corrected her problem. She subsequently kept her appointment with the neurologist to tell him of her good news. He strongly advised her to stop the medication because "there are controlled studies showing it does not work" (I am not aware of any such study) and "this drug could cause heart problems" (this is not true). She stopped the amphetamine on his advice and the headaches returned. Three months later at the urging of her husband she resumed the amphetamine and again her headaches dissipated.

Another woman with more than 20 years of severe retroorbital stabbing pain attributed to keratoconus failed to respond to bilateral corneal implants but did respond very well to dextroamphetamine sulfate [59]. A 42-year-old woman sought infertility treatment. She stated that she would have to postpone investigation for a couple months because in two weeks she was going to have an experimental procedure to break her jaw to try to ameliorate severe headaches that were present for 22 years and not only occurred every day but were present for 70% of each day. The headaches were attributed to temporal mandibular joint syndrome. The procedure was to cost her $10,000 out of pocket and she was advised it would have about a 25% chance of providing some amelioration. She was advised to try dextroamphetamine sulfate first. She had more than 90% relief in ten days so surgery was cancelled. She remains headache free on 25 mg amphetamine salts extended release capsules.

These cases show that dextroamphetamine sulfate can help some women with chronic refractory headaches but one may wonder what percentage of women fail with this therapy. We presented a series at the 2014 American Association for Clinical Endocrinologists meeting in which we evaluated this therapy in 22 consecutive women with an average duration of headaches for 13.8 years who failed to gain improvement from beta blockers, topiramate, and ergotamine preparations. Only one woman reported no improvement and stopped therapy. There were 17 of 22 (77.3%) who reported almost complete or complete relief of headaches at six months and one year of therapy. Four women reported moderate relief (data not submitted for publication yet).

Chronic fatigue syndrome

Chronic fatigue syndrome seems to be more prevalent in females than males. This condition also seems to respond very well to amphetamine therapy. Recognizing this entity can prevent a multitude of needless expensive tests and po-

tentially dangerous treatment, e.g., prolonged and several courses of antibiotics for suspected but not substantiated Lyme disease [60]. Probably the most dramatic example of correction of chronic fatigue syndrome was a woman with muscular dystrophy related to a mitochondrial disorder who was wheelchair-bound for 25 years. She walked into the office for her next visit one month after taking just 15 mg of dextroamphetamine sulfate extended release capsules. She remains corrected now for four years and walks and drives her car without fatigue [61].

We are in the process of evaluating a large series of cases with chronic fatigue syndrome, similar to our pelvic pain and headache series, and hope to present the data (which to date is very positive) at the 2016 American Association for Clinical Endocrinologists.

Fibromyalgia and inability to lose weight related to edema
Several conditions that are more prevalent in women that are refractory to other therapies but respond to dextroamphetamine sulfate include fibromyalgia [62], and inability to lose weight despite dieting (which is the only randomized controlled trial that we performed using dextroamphetamine sulfate) [63].

Other medical conditions not necessarily more prevalent in women

Other conditions refractory to standard therapy but responding extremely well to dextroamphetamine sulfate which have been described in published case reports include urticaria [64-66], long-standing eczema and keratosis pilaris [67], and pseudopheochromocytoma [68].

Other unique cases where the only therapy that corrected the condition was dextroamphetamine sulfate included restless leg syndrome, red meat allergy, post herpetic neuralgia, autoimmune hepatitis [69], hearing deficit, frozen shoulder syndrome, diplopia following orgasm [70], and a strange case of a woman who had multiple episodes per day of macroglossia which would cause her markedly enlarged tongue to protrude from her mouth and effect her speech and breathing which responded very well to the highest dosage of dextroamphetamine sulfate to date that I have prescribed – 130 mg per day (all unreported as yet).

Final thoughts

Over 20 years ago, the leading gynecologic textbook was Kistner's Textbook of Gynecology. Robert Kistner was a professor of Obstetrics and Gynecology at Harvard University and was considered for many years as one of the leading authorities in endometriosis. I remember attending a plenary lecture at the American Society for Reproductive Medicine meeting some time over 20 years ago which was given by Dr. Kistner. He stated "If a teenager has dysmenorrhea, it is malpractice if the gynecologist does not perform a laparoscopy in order to prevent the condition from getting worse and causing pelvic adhesions".

With the new information mentioned in this manuscript, I would like to make a new provocative statement: "The performance of a laparoscopy for dysmenorrhea in a teenager before trying dextroamphetamine sulfate first can be considered malpractice, especially if later the young lady is found to have diminished oocyte reserve, possibly as a consequence of laparoscopic removal of endometriosis and direct damage to ovarian tissue or indirectly by damaging ovarian blood supply".

What role does genetics play in these various permeability disorders? Indeed there may be a genetic predisposition to have certain tissues develop diminished capacity to filter out harmful chemicals, toxins and bacteria. This would explain why Crohn's disease, endometriosis, and other autoimmune diseases seem more prevalent in family members. The permeability defect can be so severe that symptoms begin in childhood. However, the defect may not manifest until later in adulthood until some acquired condition occurs, e.g., infection, trauma, or something that compromises sympathetic tone. Actually, there appears to be a genetic basis for sympathetic nervous system hypofunction. Hormonal changes can also influence permeability. This could be why the pain associated with the pelvic pain syndrome that has been previously, and in the author's opinion, erroneously, attributed to endometriosis, exacerbates at certain times of the menstrual cycle.

One can exemplify this inter-relationship between genetics, acquired illnesses, sympathetic nervous system hypofunction, and the interaction of hormones. A pre-teen girl developed abdominal pain and failure to thrive. She was diagnosed with Crohn's disease by colonoscopy and seemingly responded to mesalamine. She remained on mesalamine but developed similar symptoms in her mid 20's. However, the colonoscopy was completely negative, as were all of her annual colonoscopies since childhood. She lost 14 kg down to 33 kg. Eventually she was diagnosed as having a pseudointestinal obstruction and she responded extremely well to dextroamphetamine sulfate and fully corrected the pseudointestinal obstruction [54]. This syndrome, which appeared suddenly in her mid 20's, seemed to occur following a viral gastroenteritis that developed while on a cruise. This viral syndrome may be the acquired defect that exacerbated the genetic predisposition toward increased permeability of the small bowel and thus precipitated this problem of pseudointestinal obstruction.

Any evidence of genetic predisposition? Her mother has been treated for edema, pains in her legs with running, and unexplained loss of bladder control presumed to be related to multiple sclerosis which has been fully corrected by taking dextroamphetamine sulfate for 25 years. She had been fine from her symptoms of the sympathetic neural hyperalgesia edema syndrome but developed breast cancer and was placed on letrozole tablets post-surgery. One year later, she

developed severe shoulder pain and was misdiagnosed with the frozen should syndrome by orthopedic specialists. She failed to respond to anti-inflammatory medications, analgesics, and physical therapy. We diagnosed her with the aromatase induced arthralgia syndrome, which completely disappeared after raising her dosage of dextroamphetamine sulfate from 30 to 45 mg extended release capsules (presented at the 2015 meeting of the American Association for Clinical Endocrinology [71]. Thus, in this case, the inheritance is for the defect in sympathetic tone as opposed to a specific tissue which has an intrinsic permeability defect.

The young lady with pseudointestinal obstruction stayed on the dextroamphetamine sulfate for five years and remained in complete remission. It was discovered during her investigation of the pseudointestinal obstruction that she had hypothalamic pituitary hypothyroidism. She had already responded to the amphetamine but she was placed on thyroid hormone. After five years of remission, it was decided to try to stop the amphetamines and see if any gastrointestinal symptoms remained abated. They did for five years while she remained on thyroid hormone. We believe that the weight loss caused the low thyroid problem by reducing thyroid stimulating hormone from the pituitary to try to conserve fuel which exacerbated the defect in sympathetic tone since thyroid hormone is a sympathomimetic amine [72]. Hypothyroidism can present with many of the symptoms of the sympathetic neural hyperalgesia syndrome and this syndrome can be mistakenly diagnosed with the thyroid hormone resistance syndrome because of presentation with similar symptoms of hypothyroidism despite normal thyroid values [73].

Though her mother manifested with edema which responded to sympathomimetic amine therapy, the young lady with pseudointestinal obstruction never manifested with edema. She conceived and did not suffer from any edema until her seventh month when it gradually became extremely severe so that she gained 29 kg (she started at 45 kg). It was suggested to re-institute the dextroamphetamine sulfate but her husband, a physician, was not in favor of this therapy because of potential unknown toxic effects to the fetus coupled with the fact that she remained normotensive and without proteinuria. However, at 38 weeks her serum creatinine rose precipitously and she was heading into renal failure (1.7 mg/dL). An emergency C-section was performed and her renal function returned to normal. Thus she developed the edema part of the sympathetic neural hyperalgesia syndrome which is related to increased capillary permeability leading to increased leakage of fluid from intravascular to extra-vascular space and the rennin-angiotensin aldosterone back-up system was not able to compensate for the loss of intravascular fluid leading to insufficient renal perfusion. Alternatively, chemicals related to increased cellular permeability may have caused decreased kidney function similar to her two previous bouts of decreased small bowel function. This case exemplifies that high levels of estrogen and/or progesterone can increase capillary permeability supporting the association of hormones and the sympathetic neural hyperalgesia edema syndrome.

Future perspectives

It is very likely that anyone reading this perspective who decides to treat the various mentioned disorders with dextroamphetamine sulfate will be very pleased with the outcome. Nevertheless, it is highly unlikely that this therapy will be widely used in the next five to ten years. The reason for this statement is, in general, widespread use of a drug generally requires a wide-spread advertisement campaign by pharmaceutical companies hoping to make a profit from a new drug. There are no pharmaceutical companies hoping to make a profit from dextroamphetamine sulfate for off-label use and there are no pharmaceutical companies promulgating this therapy.

It is unlikely that despite its efficacy and safety, any pharmaceutical company, including the present day manufacturers, will promote it because the drug is already available as a generic. Thus, there does not appear to be a potential profit in exchange for expenditure. The previous publications over 30 years would make it difficult to acquire a patent.

More widespread use, and thus help for a greater proportion of women (and men, too) who are needlessly suffering and not responding to "conventional" therapy can only increase in a limited manner by word of mouth. One way is to present the data at research meetings which usually frown on case reports but sometimes accept a series of cases. Another method is through publications and that is the motive behind writing this perspective: to provide one concise summary of other publications and to provide new anecdotes and a better perspective of this disorder.

Some physicians will only prescribe a new drug or use a new treatment that has been proven by a randomized controlled trial (RCT). Ethically and socioeconomically, I cannot perform one, though, I would do so if a company was willing to fund such a study not to gain more personal income but with the thought that demonstration of efficacy in an RCT will convince more physicians to adopt this treatment. Possibly, this article will stimulate some of the readership to conduct such a trial, and with their likely publication of the superiority of sympathomimetic amine therapy, more physicians will be convinced to try this therapy on patients resistant to standard therapy for pelvic pain, other pain symptoms, chronic fatigue, gastrointestinal motility disorders, and various skin conditions especially urticaria. I believe that those of you willing to try this treatment for the conditions described will be greatly rewarded. It may completely revolutionize your method of practice. If you share the same enthusiasm (after trying sympathomimetic amine therapy) (or if you do not), please publish your findings. Credibility increases if all the publications do not seem to come from just one center.

Potential new uses

It seems logical that this disorder of cellular permeability by possibly allowing unwanted chemicals to infuse into the endometrium with subsequent inflammation may be associated with an inflammatory endometrium leading to implantation failure (infertility or miscarriage). Our practice is geared toward evaluating a retrospective series, matched controlled study or even a randomized controlled study evaluating efficacy of sympathomimetic amine therapy for infertility and recurrent miscarriage.

Anecdotally, we have seen marked improvement in pregnant women with edema following treatment with dextroamphetamine sulfate. With all of the advancement in modern medicine, there is still not a good therapy for the prevention or treatment of pre-eclampsia. We only treat women through the first trimester. It is unlikely that we will have the opportunity to initiate a study for the prevention of pre-eclampsia with dextroamphetamine sulfate. Hopefully, this manuscript will interest some obstetrics and gynecology specialists to try this therapy for this condition and either publish case reports or randomized controlled studies.

Along the same lines, it seems reasonable that the abrupt rise in estrogen and/or progesterone with the ovarian hyperstimulation syndrome (OHSS) can cause marked edema and even anasarca in certain women, who already may have slightly compromised sympathetic tone, but sufficient sympathetic activity to preclude any clinical symptoms until there is further compromise by the new change in hormonal status. It serves to reason, therefore, that dextroamphetamine sulfate could be used to prevent or ameliorate OHSS. We have used this drug in circumstances of women following controlled ovarian hyperstimulation with more than 25 stimulated follicles and/or serum estradiol levels > 5,000 pg/mL but have never published any anecdotes because not all women who reach these criteria develop OHSS. Thus, we cannot state with certainty that failure to develop OHSS was because of ingesting the dextroamphetamine sulfate. Similar to the woman with the aromatase induced arthralgia syndrome, we have had many cases who seem to run a very benign course over the years of multiple sclerosis following sympathomimetic amine therapy, despite a more rocky early course pre-treatment. However, because of the nature of the disorder with long remissions, we can not state for sure the benign course was related to treatment with amphetamine.

Recently, the drug onansetron has been questioned as to its safety in treating nausea and hyper-emesis of pregnancy. Related to this, we will be offering treatment with amphetamine for severe nausea and vomiting during the first trimester (we generally follow the women for their first trimester). On what basis rests our optimism that amphetamine will relieve this type of suffering? One of the female medical students on an office rotation kept excusing herself to go to the bathroom. I inquired if she was alright and she said yes, she has emesis multiple times each day related to untreatable gastroparesis. She had suffered for ten years and was used to the symptoms. All her vomiting disappeared within two days of taking the dextroamphetamine sulfate.

There is a possibility that the rise in various hormones during pregnancy increases cellular permeability of the stomach in some people and if combined with some degree of sympathetic nervous system hypofunction those women may develop a type of gastroparesis or at least diminished stomach motility with resulting nausea and vomiting. The theory is that improving sympathetic tones will diminish the increase permeability of the mitochondria of gastrointestinal smooth muscle which was responsible for diminished gastric motility leading to nausea and vomiting.

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