Review Article ISSN 2639-944X

Journal of Medical - Clinical Research & Reviews

Various Presentations of The Increased Cellular Permeability Syndrome in Males Responding Very Well to Sympathomimetic Amine Therapy – Possible Treatment for End-Stage Covid-19 Complications

Diane L Check[1] and Jerome H Check[1,2*]

[1]*Cooper Institute for Reproductive Hormonal Disorders, P.C., MT. Laurel, NJ, USA.*

[2]*Cooper Medical School of Rowan University, Dept. Ob/Gyn, div. Repro. Endo. & Infertility, Camden, NJ, USA.*

***Correspondence:**
Jerome H. Check, M.D., Ph.D., Cooper Medical School of Rowan University, Dept. Ob/Gyn, div. Repro. Endo. & Infertility, Camden, NJ, USA, Tel: 215-635-4400; Fax: 215-635-2304.

Received: June 2020; **Accepted:** July 2020

Citation: Diane L Check, Jerome H Check. Various Presentations of The Increased Cellular Permeability Syndrome in Males Responding Very Well to Sympathomimetic Amine Therapy – Possible Treatment for End-Stage Covid-19 Complications. J Med - Clin Res & Rev. 2020; 4(7): 1-7.

ABSTRACT

There is a disorder known as the increased cellular permeability syndrome that is a common cause of various chronic disorders. Though common, it is relatively unknown to most treating physicians. Excessive infiltration of irritants into various tissues can cause inflammation and pain, cause organ dysfunction leading to various symptoms, e.g., diarrhea, or infusion into smooth and skeletal muscle leading to disorders related to muscle dysfunction, or leaking out of substances from cells that should be contained, thus, causing urticaria, anaphylaxis, and edema. All these conditions have in common the fact that they all respond very well to treatment with dextroamphetamine sulfate despite resistance to standard therapy. The large majority of case reports and series have been reported in women. The present study demonstrates the efficacy of sympathomimetic therapy for a wide variety of clinical manifestations that were found in men. Several of the cases reported to improve greatly following dextroamphetamine sulfate treatment have never been previously reported in women.

Keywords

Covid-19, Gastrocolic reflex, Hereditary spastic paraplegia, Increased cellular permeability syndrome, Mesenteric sclerosis.

Introduction

Increased cellular permeability is a common problem in women leading to a wide variety of clinical manifestations [1,2]. It has been hypothesized that these various clinical manifestations are related to relative hypo-function of the sympathomimetic nervous system [3,4]. Sympathetic nerve fibers release dopamine, which, in turn, diminishes cellular permeability [1-4].

The various published case reports demonstrating tremendous relief of a wide variety of pathologic conditions in women by the sympathomimetic amine dextroamphetamine sulfate, even those entities that had been refractory to standard therapy, has been attributed to the increased release of dopamine from sympathetic nerve fibers following dextroamphetamine therapy [1-4]. Though many of these pathological entities had been persistent throughout the menstrual cycle, some were exacerbated, or only present, during the luteal phase, or during menses, e.g., dysmenorrhea, dyspareunia, headaches, urticaria, interstitial cystitis and even Crohn's disease [5-10].

The pre-menstrual exacerbation of some of these pathological state has been attributed to the role of progesterone in inhibiting dopamine secretion leading to a purposeful infiltration of irritants into the endometrium to establish an inflammatory state to enable uterine artery remodeling, especially the conversion of some of the thick-walled uterine arteries into thin-walled spiral arteries, to allow nutrient exchange between mother and fetus [11].

Though the very common (but still relatively unknown) increased cellular permeability syndrome is more common in women, this entity does plague males also. The present study reports various pathological states in men that were refractory to standard therapy that responded extremely well to treatment with dextroamphetamine sulfate.

Case Report

Case 1 – Severe constant headaches following multiple concussions

A 22-year-old male was referred by his girlfriend whose migraine headaches had been helped to a great degree by treatment with dextroamphetamine sulfate. She referred her boyfriend whose headaches never existed before his first concussion playing college ice hockey.

They became more severe and more frequent occurring every day for a large part of each day after his 7th concussion. His last concussion occurred 2 years prior to his appointment.

There had many therapies and strong analgesics prescribed by neurologists and headache specialists, but no therapy to date abated his headaches adequately. His treatment included several ergotamine preparations, topiramate and beta blockers.

This young man showed considerable improvement at his one-month evaluation after taking amphetamine salts 15mg extended release capsules containing 9.4mg dextroamphetamine sulfate. By increasing the dosage to 18.8mg dextroamphetamine sulfate extended release capsules, he rarely experiences any headaches. In fact, if one occurs, it is very mild. The beneficial effect has persisted for 3.8 years.

Case 2 – Severe constant headaches following 17 brain surgeries for a choroid plexus papilloma

A 20-year-old male with a history of 17 surgical procedures since age 16for a choroid plexus papilloma including craniotomies, and ventriculoperitoneal shunts, 6 cyst draining procedures, and ventriculostomy, was given the news that the tumor was finally surgically corrected. However, as a complication, he was left with constant unremitting headaches always present. (except during sleep) for 3 ½ years. Beta-blockers, topiramate and anabotulinum toxin A (botox®) injections were ineffective. The headaches were described as severe and constant.

He was advised that dextroamphetamine sulfate was found to be very effective in women for headaches that were refractory to conventional therapy [12-17]. He was treated with amphetamine salts 15mg extended release capsules daily which contains 9.4mg dextroamphetamine sulfate. Within 1 hour of taking the dextroamphetamine sulfate, his headaches disappeared and has not returned in 3 years, except for 1 week when he ran out of medication, and the headaches resumed immediately. Nevertheless, they stopped immediately again once resuming the dextroamphetamine sulfate.

The young man had stated that prior to surgery he rarely ever had headaches.

Case 3 – Severe abdominal pain and vomiting from mesenteric sclerosis

For a 4-year time span, a 47-year-old male developed severe abdominal pain within 5 minutes after eating. The pain was so intense that this very tough longshoreman would need to roll on his back, throw his legs up, because the pain was so intense. It frequently induced screaming and crying. He also complained of vomiting at least 20 times per day. He had lost 70 pounds during this year. The pain was getting progressively worse. Additionally, he had joint pain in his knees from psoriatic arthritis.

Despite being evaluated by many gastroenterologists at major University centers, his diagnosis remained obscure. He consulted our group after being referred by his family physician who had referred other patients where they obtained pain relief following sympathomimetic amine therapy.

He postponed the appointment because he obtained an appointment to be evaluated at the world-renowned Mayo Clinic in Rochester, Minnesota. After multiple tests, they concluded by intestinal biopsy that he had a severe form of the rare condition known as mesenteric sclerosis. They explained to him that when he eats it diverts the blood supply to the gastric arteries to help digest the food, and in so doing, it draws blood away from the mesenteric arteries, thus causing bowel ischemia.

Unfortunately, they could not offer any advice for treatment other than eat extremely small portions. He was already eating very tiny portions and was still getting the severe pain. They told him that he was likely to die within the year related to bowel perforation and sepsis.

Treatment with 9.4mg dextroamphetamine sulfate in the form of 15mg extended release capsules of amphetamine salts was offered. If this dosage did not make the problem worse, but did not help either, the plan was to raise the dosage gradually, unless there was no improvement following 60mg, when therapy would be stopped.

The man stated that within the first couple days of treatment his severe stabbing and shooting abdominal pain with eating was completely gone. He noted that he did not have one day of relief prior to treatment in 4 years. His vomiting was reduced from over 20 times per day to 1-2 times per day. His only side effects were dry mouth (common) and diminished libido (uncommon).

He was offered to raise the dosage of dextroamphetamine sulfate to see if it could help the joint pain. However, he declined for fear it would diminish his libido more, and he said the joint pain was tolerable. He has remained symptoms free from abdominal pain and vomiting, with no food intolerance, for 6 years. His joint pain has improved by at least 50% despite a relatively small dosage of dextroamphetamine sulfate.

Case 4 – Widespread long-standing very severe multi-focal pain resulting from multiple bone fractures

A 45-year-old male, who was an ex-marine, sought a medical opinion as to whether sympathomimetic amine therapy could provide him some degree of relief from chronic severe pain that he was experiencing.

The chronic pain in multiple areas of his body was attributed to multiple injuries he received during the Gulf War in 1993 including a stabbing wound in the neck, a gunshot wound in the leg, and multiple fractures in his jaw, ankles, knees, and vertebrae that resulted from being hit by an improvised explosive device (IED). The injuries caused by the IED led to a prolonged hospitalization and finally his retirement from the marines in 1993. Thus, this man had been suffering from severe pain for 24 years when he consulted our group.

He had multiple surgical procedures performed on both his right and left knees and his most recent operation had been on his left knee 3 years prior to his initial visit.

The worst pain was in his axial neck and low back. The low back pain was the most limiting pain radiating down the left leg into the toes, not only with walking, but sharp shooting pain even at rest. The pain intensity scale over the month prior to his visit ranged from 6-10 with an average of 8. This was despite being treated with various opiate pain relievers. This degree of pain was present despite his treatment with oxycontin 30mg extended release tablets every 12 hours, and oxycodone tablets 10mg every 8 hours. Other drugs included oxycodone extended release capsules sprinkle 36mg and hydrocodone bitartrate extended release tablets. He previously had multiple injections of methylprednisolone acetate into joints that failed to provide anything but transient relief.

He was started on 9.4mg dextroamphetamine immediate release tablets twice daily. He had such improvement within the first couple of days he started to wean himself off the opiate drugs. Without the oxycodone and oxycontin, his pain decreased from an average score of 8 out of 10 to 5 out of 10. However, with an increase to 18.8mg twice daily of dextroamphetamine immediate release tablets, his pain decreased to mostly zero, occasionally a score of 1 and rarely a score of 2. He has been relatively pain free for 3 years and has not taken even one time any other analgesics.

He also suffered from chronic fatigue syndrome and restless legs syndrome. He had been told that these conditions may have been related to his exposure to sarin gas. Interestingly, both the chronic fatigue and restless legs syndrome disappeared while taking sympathomimetic amines. The restless legs syndrome was so severe he ripped the sheets so bad that they had to be replaced weekly. Previously he failed to demonstrate any benefit in his restless leg syndrome despite treatment with ropinirole and pramipexole.

Case 5 – Gastroparesis

A 46-year-old man complained of nausea, vomiting, abdominal distention, and abdominal pain. Based on a delayed gastric emptying time, he was diagnosed with gastroparesis. Various drugs were tried for symptomatic relief, but not only were they not effective, they all were associated with severe side effects. For example, metoclopramide caused severe burning throughout this body associated with erythema of the neck and chest, and also severe headaches. This led to evaluating for reasons for his drug sensitivity, and he was found to have abnormal drug metabolism. A heterozygous CPY2D6*41 reduced activity variant was diagnosed.

Treatment with domperidone was tried, and initially, this drug seemed to provide relief. However, over time, it lost its efficacy and all symptoms returned and domperidone was stopped.

At age 53 he consulted our practice. Treatment with dextroamphetamine sulfate as a treatment for gastroparesis was now suggested. However, in view of the heterozygous CYP2D6*41 reduced activity variant a marked reduced starting dosage was used (5mg) extended release capsule (15mg amphetamine salts [9.4mg dextroamphetamine sulfate] is the usual starting dosage).

The dextroamphetamine sulfate 5mg extended release capsules completely relieved his gastrointestinal symptoms within one day of taking the amphetamine. However, because of chest pain and hypertension he stopped the medication (he had a history of coronary artery disease), and the gastrointestinal symptoms quickly returned.

His cardiologist placed him on 500mg ranolazine for his coronary artery disease. He then tried 2.5mg dextroamphetamine sulfate (1/2 of 5mg tablet) and it also proved effective for his gastrointestinal symptoms. His gastroparesis has been under adequate control for 8 years without any cardiac side effects.

Case 6 – Parkinson's Disease

A 42-year-old male was diagnosed with Parkinson's disease, based on clinical symptoms of weakness of his left arm with stiffness, so that it was not swinging with walking. He also dragged his right foot. Clinical signs suggested Parkinson's and an MRI ruled out other pathological conditions. A tremor was also found in the left arm. He also complained of pain in the mid and upper back.

However, his most troubling symptom was marked fatigue. He was started on 15mg amphetamine extended release capsules. In one month, he noticed significant improvement in his fatigue and muscle stiffness. His pain in his neck and upper back were also abrogated. He failed to note any improvement in the tremor.

He was now able to pick up his newborn baby when he was unable to do so before. Improved clinical status has remained stable for 4 years 7 months. There has not been any worsening of the tremors while he continues the 9.4 mg dextroamphetamine extended release capsules once daily.

Case 7 – Hereditary spastic paraplegia

A 45-year-old man was diagnosed with hereditary spastic paraplegia syndrome by his neurologist. The diagnosis was made based on the fact that his 59 year old brother has this condition (and the type he had was considered a familial type related to an autosomal dominant form of this disease) and based on the patient's physician examination, which demonstrated an abnormal spastic gain, and weakness in his lower extremities controlled by his iliopsoas muscle and tibialis anterior muscle causing him to drag his right leg.

He was offered treatment with dextroamphetamine sulfate therapy extended release capsule. Upon his return visit one month later after treatment with 18.8mg dextroamphetamine, the patient noted a complete reversal of his symptoms with full return of his muscle strength. This allowed him to participate in strenuous physical activity, e.g., hill climbing and bicycle riding. His gait was perfectly normal, and he no longer dragged his leg. The patient has maintained this improvement with very little progression, 5 years on amphetamine therapy.

Case 8 – Gastrocolic reflex

A 20-year-old male was referred for severe gastrocolic reflex and recurrent aphthous stomatitis (RAS).

He stated that since puberty he would have to defecate immediately after eating, not just occasionally, but every time he would eat. It progressively got worse so that at the time of his consultation, more often than not, he had to leave the table to defecate during the meal. The symptoms included moderately severe abdominal pain, and if there was no bathroom present, he would have "an accident" and defecate in his pants.

He was started on 15mg extended release amphetamine salts, providing 9.4mg of dextroamphetamine sulfate, which immediately ameliorated his gastrocolic reflex. The dosage was titrated to 25mg extended release capsules, providing 15.5mg of dextroamphetamine sulfate. This therapy has completely eradicated his gastrocolic reflex problem.

Over the four years of treatment, he has not had one episode of RAS. In the past his RAS episodes would be present about 25% of the year.

Case 9 – Vasomotor instability and abnormality of the temperature regulation system

Since puberty at age 12, a male complained of sudden episodes of an intense feeling of great heat throughout his body. The heat sensation was so severe that it felt as if his body was on fire. He had been given permission in high school to immediately leave the room, where he would go to the men's room, remove his clothes, and douse himself with water to put the fire out.

These episodes were occurring more frequently and at the age of 16 he sought medical help from our group. With 9.4mg twice daily of dextroamphetamine sulfate he has not had even one more heat episode in 6 years.

Discussion

Cases 1 and 2 showed marked improvement of severe intractable headaches following brain trauma. There have been many case report publications concerning the beneficial effect of dextroamphetamine sulfate including idiopathic migraine headaches [12,13], ocular migraines [7,16], and headaches from temporomandibular joint syndrome [17]. There has also been a case report of dextroamphetamine sulfate markedly improving severe constant headaches that were present in two teenage girls even 6 months after a school bus accident with severe concussion. What is interesting was that not only did the headaches disappear immediately in these two teenage girls, but so did their severe stuttering [18].

Case 2 is a unique case in that there has never been a case report in a woman or man that had intractable treatment refractory severe headaches resulting from multiple brain surgeries that immediately dissipated following sympathomimetic amine therapy.

Case 3, who showed dramatic relief from severe abdominal pain from mesenteric sclerosis following dextroamphetamine sulfate, is unique and this treatment has never been tried in any of the rare 400 cases reported, whether male or female. He is probably one of the worst clinical presentations of this very rare disorder.

Case 4 is another case of dramatic pain relief after 25 years of pain where a man was getting no relief from high dosage opiates and multiple surgeries. It was also amazing how quickly the man was able to stop opiates. Perhaps the pain was related to chronic regional pain syndrome (reflex sympathetic dystrophy). There is a case report of a woman with chronic regional pain syndrome also responding very well to dextroamphetamine sulfate therapy [19]. As far as the severe chronic fatigue syndrome in case 4, this has been published as a case report in a woman [20].

As far as his restless legs syndrome, we believe he is the first published case showing marked improvement with dextroamphetamine sulfate when standard therapy had failed. However, one case was presented at the Annual Meeting of the American Association for Clinical Endocrinologists (AACE) in 2015, with the abstracts published in the Endocrine Practice journal also demonstrating relief of restless legs syndrome in a woman who failed standard therapy. The case of the restless legs syndrome in this ex-marine was the most severe with the leg movements so violent that new sheets were needed weekly.

According to the tenets of the increased cellular permeability syndrome concept, increased cellular permeability may be intrinsic and represent a genetic predisposition for the increased cellular permeability in a certain organ system leading to abnormal infiltration of irritants into that tissue causing inflammation and pain. The increased permeability may also be as a result of trauma, as seen in the two men with severe headaches following multiple concussions or multiple brain surgeries, or pain in other areas as seen in the man with the multiple bone fractures hit with an IED.

The increased permeability may be related to infection leading to increased permeability. In some cases, the increased permeability may be in sensory nerve fibers leading to irritation and pain. There has been a published case of an 88-year-old male with a 5-year history of extremely severe post-herpetic neuropathy, that not only failed to respond to the standard anti-neuropathy drugs, but the pain also barely lessened with opiates. The pain completely dissipated shortly after being treated with dextroamphetamine sulfate. He subsequently lived a pain-free life and died in his sleep

at age 93 [21].

It is not clear how food ingestion caused the severe abdominal pain in the man with mesenteric sclerosis. If the explanation provided by the specialists at the Mayo Clinic was correct, it is not clear how the dextroamphetamine sulfate was able to obviate vascular insufficiency. Rather ingestion of food may have triggered increased permeability of smooth muscles of the intestines leading to inhibition of normal function. In a female with marked weight loss and abdominal pain related to pseudointestinal obstruction, her pain symptoms immediately disappeared, and she was able to resume her normal weight following treatment with dextroamphetamine sulfate [22].

Case 5, with another motility disorder of the gastrointestinal system, i.e., gastroparesis, also had moderate to severe abdominal pain. Again, the hypothesis was that increased cellular permeability of his gastrointestinal smooth muscle allowing irritants to infiltrate mitochondria caused muscle dysfunction leading to decreased motility. The mechanism could be that the nerves innervating the gastric smooth muscle did not release sufficient dopamine to prevent increased cellular permeability. Alternatively, some type of genetic defect or damage, e.g., infection, created an increased gastric muscle permeability disorder requiring a greater secretion of dopamine from sympathetic nerve endings. In either case dextroamphetamine sulfate, by releasing more dopamine, corrected the problem.

The first case report of treating gastroparesis with dextroamphetamine sulfate was published in 2007 in a woman [23]. The male reported here was unique because he also had a genetic problem being heterozygous for the CYP2D6*41 reduced activity variant causing him to have severe side effects to normal low dosage dextroamphetamine sulfate therapy. This is the only person to date with a significant medical problem that had to reduce the dosage of amphetamine salts to only 2.5mg per day. This provides only 1.6mg dextroamphetamine sulfate. Interestingly, the opposite was seen in another patient with gastroparesis who over metabolized dextroamphetamine sulfate. Thus, this woman showed no benefit (or side effects) to 120 mg of amphetamine salts (equal to 74 mg dextroamphetamine sulfate) but had total resolution of her problem following 92.5 mg of dextroamphetamine sulfate [24].

It is well known that Parkinson's disease is associated with dopamine deficiency. Thus, it is not surprising that a drug that releases more dopamine from sympathetic nerve fibers can improve symptoms of Parkinson's disease, as in Case 6, unless there is total depletion of dopamine. Perhaps diminished dopamine secretion is sometimes related to hereditary spastic paraplegia and could explain how dextroamphetamine sulfate treatment seemed to have halted the progression of this disorder in Case 7.

Dextroamphetamine sulfate has been found to markedly improve several other neurological disorders. One woman had severe paresis and was wheelchair ridden for 25 years related to the mitochondrial encephalopathy lactic acid stroke-like syndrome who was able to walk normally within 2 months of treatment with dextroamphetamine sulfate [25]. Another woman, who had a severe case of neurogenic bladder, refractory to standard therapy, had complete correction of the problem with dextroamphetamine therapy [26].

Sympathomimetic amine therapy not only treats the pain from various gastrointestinal disorders, but also severe diarrhea as found in Crohn's disease or ulcerative colitis, or microscopic colitis [8,10,27,28]. Sometimes the inflammatory bowel disease is associated with other manifestations of the increased cellular permeability syndrome, e.g., manifestation of endometriosis (dysmenorrhea, chronic pelvic pain, and mittelschmerz) [8]. Sometimes pain and diarrhea are triggered by food, e.g., an unreported case of red meat allergy also corrected by treatment with dextroamphetamine sulfate. Case 8, of a young man with gastrocolic reflex, had no evidence of inflammatory bowel disease by colonoscopy, but similar to some of these inflammatory bowel conditions, had abdominal pain and the need to defecate when food was introduced to his alimentary system. This the first case of using dextroamphetamine sulfate to treat gastrocolic reflex in a male or female.

There is no question that vasomotor instability is associated with women with estrogen deficiency, especially when there is simultaneous elevation in gonadotropins related to ovarian failure. Estrogen has been the main effective treatment. However, in some instances, estrogen cannot be used, and it has been found that dextroamphetamine sulfate can be an effective alternative therapy [29]. However, it was found that sympathomimetic amine therapy was also very effective for a younger woman with normal estrogen and normal day 3 follicle stimulating hormone [30]. Case 9 is the first reported case of a male with extremely severe vasomotor instability and abnormality with the temperature regulation center of the brain responding quite well to dextroamphetamine sulfate treatment.

It is interesting that Case 9 and his brother, who was Case 8, had a sister, who besides chronic fatigue, dysmenorrhea, and edema, also had extremely severe recurrent aphthous stomatitis (RAS) since early childhood. She presented with over 50 mouth ulcers daily for 20 years until treatment with dextroamphetamine amine [31]. It is interesting that Cases 8 and 9 also suffered from RAS, but not to the same degree as their sister.

Increased cellular permeability may be intrinsically involved in the clinical manifestations of other autoimmune entities [32-34]. Possibility the role of progesterone in suppressing dopamine may make women more prone to increased cellular permeability and autoimmune conditions. However, as demonstrated by these 9 case reports, men may also suffer from various manifestations of this syndrome. Similar to their female counterparts, they also respond very well to treatment with dextroamphetamine sulfate.

The world in 2019 has been faced with the COVID-19 pandemic. A small percentage who contract the disease will rapidly progress

to death. There has been some evidence that people who have been taking anti-hypertensive medications especially angiotensin converting enzyme (ACE) inhibitors may be protected from the deadly manifestations of this coronavirus [35-41]. The angiotensin converting enzyme has been implicated in one of the clinical presentations of the increased cellular permeability syndrome, namely, the capillary leak syndrome leading to peripheral edema and weight gain [35,42,43]. In a randomized controlled study with a cross-over, dextroamphetamine sulfate treatment was far more effective in preventing edema and weight gain than the ACE inhibitor captopril (and also spironolactone, and hydrochlorothiazide [44].

There is a possibility that the COVID-19 virus is causing an acute increase in cellular permeability predominantly in the lungs but including other organs by the inflammatory response induced by infiltration of unwanted toxic chemicals into these tissues. In view of the wide variety of medical conditions refractory to standard therapy, but responding very well to dextroamphetamine sulfate, it is hoped that this manuscript may encourage a trial of dextroamphetamine sulfate for people who seem to be at risk for rapid progression and death from Covid-19. The drug has proved to be safe and well tolerated even in people of advanced age as in the aforementioned case of an 88-year-old man with severe post-herpetic neuralgia who responded quickly and effectively with great tolerance until his death at age 93 [21].

References

1. Check JH. Changing the name of a syndrome Sympathetic neural hyperalgesia edema syndrome becomes-the increased cellular permeability syndrome. Clin Exp Obst Gyn. 2017; 44: 819-823.
2. Check JH. Sympathomimetic amines are a safe, highly effective therapy for several female chronic disorders that do not respond well to conventional therapy. Clin Exp Obst Gyn. 2015; 42: 267-278.
3. Check JH, Katsoff D, Kaplan H, et al. A disorder of sympathomimetic amines leading to increased vascular permeability may be the etiologic factor in various treatment refractory health problems in women. Med Hypoth. 2008; 70: 671-677.
4. Check JH, Cohen R, Katsoff B, et al. Hypofunction of the sympathetic nervous system is an etiologic factor for a wide variety of chronic treatment-refractory pathologic disorders which all respond to therapy with sympathomimetic amines. Med Hypoth. 2011; 77: 717-725.
5. Check JH, Wilson C. Dramatic relief of chronic pelvic pain with treatment with sympathomimetic amines-case report. Clin Exp Obst Gyn. 2007; 34: 55-56.
6. Check JH, Katsoff B, Citerone T, et al. A novel highly effective treatment of interstitial cystitis causing chronic pelvic pain of bladder origin case reports. Clin Exp Obst Gyn. 2005; 32: 247-249.
7. Check JH, Cohen R. The triad of luteal phase ocular migraines interstitial cystitis and dyspareunia as a result of sympathetic nervous system hypofunction. Clin Exp Obst Gyn. 2014; 41: 575-577.
8. Check JH. Increased tissue permeability and sympathetic nervous system hypofunction may be the common link between dysmenorrhea chronic pelvic pain Mittelschmerz and Crohn's disease. Clin Exp Obst Gyn. 2016; 43: 112-113.
9. Check JH, Dougherty MP. Use of sympathomimetic amines to correct premenstrual urticaria and anaphylaxis. Clin Exp Obst Gyn. 2019; 46: 309-312.
10. Check JH, Katsoff B, Cohen R. A novel highly effective medical treatment of severe treatment refractory Crohn's disease using sympathomimetic amines-case report. Inflam Bowel Dis. 2010; 16: 1999-2000.
11. Check JH, Aly J, Chang E. Improving the chance of successful implantation-part I – embryo attachment to the endometrium and adequate trophoblast invasion. Clin Exp Obst Gyn. 2016; 43: 787-791.
12. Check JH, Check D, Cohen R. Sympathomimetic amine therapy may markedly improve treatment resistant headaches related to a vascular permeability defect common in women. Clin Exp Obst Gyn. 2009; 36: 189-191.
13. Check JH, Cohen R, Check D. Evidence that migraine headaches in women may be related to a common defect in the sympathetic nervous system as evidenced by marked improvement following treatment with sympathomimetic amines. Clin Exp Obst Gyn. 2011; 38: 180-181.
14. Check JH, Cohen R. Severe headaches from intracranial hypertension pseudotumor cerebri abrogated by treatment with dextroamphetamine sulfate. Clin Exp Obst Gyn. 2014; 41: 211-213.
15. Check JH, Cohen R. Marked improvement of headaches and vasomotor symptoms with sympathomimetic amines in a woman with the sympathetic hyperalgesia-edema syndrome. Clin Exp Obst Gyn. 2011; 38 :88-89.
16. Check JH, DiAntonio G, Cohen R. Dextroamphetamine sulfate, a very effective drug for pelvic pain relieved severe retroorbital stabbing pain in a woman with keratoconus who failed to respond to bilateral corneal implants. Clin Exp Obst Gyn. 2014; 41: 80-82.
17. Check JH. Dextroamphetamine sulfate treatment eradicates long-term chronic severe headaches from temporomandibular joint syndrome-a case that emphasizes the role of the gynecologist in treating headaches in women. Clin Exp Obst Gyn. 2016; 43: 119-122.
18. Check JH, Citerone M, Citerone T. The increased cellular permeability syndrome as a cause of traumatic stuttering. Clin Exp Obst Gyn. 2018; 45: 773-774.
19. Check JH, Cohen R. Sympathomimetic amine therapy found effective for treatment of refractory chronic complex regional pain syndrome reflex sympathetic dystrophy. Clin Exp Obst Gyn. 2014; 41: 478-482.
20. Check JH, Cohen R. Sympathetic neural hyperalgesia edema syndrome, a frequent cause of pelvic pain in women, mistaken for Lyme disease with chronic fatigue. Clin Exp Obst Gyn. 2011; 38: 412-413.
21. Check JH, Dougherty MP, Check DL. Long standing post-herpetic neuralgia resistant to standard anti-neuropathy

medication showing quick dramatic improvement following treatment with sympathomimetic amines. Clin Exp Obst Gyn. 2019; 46: 335-336.
22. Check JH, Cohen R. Successful treatment of a female with chronic pseudo-intestinal obstruction with sympathomimetic amines and thyroid hormone replacement. Clin Exp Obst Gyn. 2010; 37: 115-116.
23. Boimel P, Check JH, Katsoff D. Sympathomimetic amine therapy may improve refractory gastroparesis similar to its effect on chronic pelvic pain-case report. Clin Exp Obst Gyn. 2007; 34: 185-187.
24. Check JH, Cohen R. Marked improvement of severe gastroparesis following high dosage, but very well tolerated, dextroamphetamine sulfate. Clin Exp Obst Gyn. 2017; 44: 611-612.
25. Potestio CP, Check JH, Mitchell-Williams J. Improvement in symptoms of the syndrome of mitochondrial encephalopathy, lactic-acidosis, and stroke-like symptoms MELAS following treatment with sympathomimetic amines-possible implications for improving fecundity in women of advanced reproductive age. Clin Exp Obst Gyn. 2014; 41: 343-345.
26. Check JH, Check D. The increased cellular permeability syndrome manifesting as severe idiopathic type urinary incontinence. Clin Exp Obst Gyn. 2019; 46: 812-814.
27. Check JH, Katsoff B, Cohen R. A case report showing that a woman with ulcerative colitis refractory to standard therapy responded well to the sympathomimetic amine dextroamphetamine sulfate. Inflam Bowel Dis. 2011; 17: 870-871.
28. Check JH, Cohen R. Sympathomimetic amine therapy abrogates severe long-term unexplained abdominal pain and diarrhea microscopic colitis-possible infertility implications. Clin Exp Obst Gyn. 2019; 46: 489-491.
29. Check JH, Cohen R, Check D. A novel highly effective therapy for severe vasomotor symptoms in an estrogen deficient woman – case report. Clin Exp Obst Gyn. 2010; 37: 229-230.
30. Check JH, Katsoff D, Kaplan H. Idiopathic orthostatic cyclic edema as a unique etiology for vasomotor flushing in a normal estrogenic woman with normal day 3 follicle stimulating hormone-case report. Clin Exp Obst Gyn. 2006; 33: 125-126.
31. Present SI, Check JH. Hypofunction of the sympathetic nervous system as a possible etiologic cause of recurrent aphthous stomatitis. Compendium. 2016; 37: 1-7.
32. Boimel P, Check JH. Marked improvement of intractable arthritic pain in a woman with rheumatoid arthritis with sympathomimetic amine treatment despite previous failure with standard therapy and possible implications for last trimester unexplained fetal demise-case report. Clin Exp Obst Gyn. 2007; 34: 254-256.
33. Weidner J, Check JH. Marked improvement of the autoimmune syndrome associated with autoimmune hepatitis by treatment with sympathomimetic amines. Clin Exp Obst Gyn. 2014; 41: 460-461.
34. Check JH. Sympathetic neural hyperalgesia edema syndrome as a cause of autoimmune hearing loss. Clin Exp Obst Gyn. 2017; 44: 133-134.
35. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. Hypertens Res. 2020; 27: 1-7.
36. Lopes RD, Macedo AVS, de Barros E Silva PGM, et al. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 SARS-CoV-2. Am Heart J. 2020; 226: 49-59.
37. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-Converting Enzyme 2 SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res. 2020; 126: 1456-1474.
38. Li Y, Zhou W, Yang L, et al. Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. Pharmacol Res. 2020; 157: 104833.
39. Kreutz R, Algharably EAE, Azizi M, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. Cardiovasc Res. 2020.
40. Mancia G, Rea F, Ludergnani M, et al. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med. 2020; 382: 2431-2440.
41. Rossi GP, Sanga V, Barton M. Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients. Elife. 2020; 9: e57278.
42. Docci D, Turci F, Salvi G. Therapeutic response of idiopathic edema to captopril. Nephron. 1983; 34: 198-200.
43. Suzuki H, Fujimaki M, Nakane H, et al. Effect of the angiotensin converting enzyme inhibitor, captopril SQ14.225 on orthostatic sodium and water retention in patients with idiopathic oedema. Nephron. 1985; 39: 244-249.
44. Check JH, Shanis BS, Shapse D, et al. A randomized comparison of the effect of two diuretics a converting enzyme inhibitor and a sympathomimetic amine on weight loss in diet-refractory patients. Endoc Pract. 1995; 1: 323 326.