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Marked Improvement of Nightmare Disorder and Backaches Following Treatment with Amphetamine Salts

Check Jerome H[1,2]*, Neumann Brooke A[3] and Check Diane L[2]

[1]*Cooper Medical School of Rowan University Camden, New Jersey, USA.*

[2]*Cooper Institute for Reproductive Hormonal Disorder, Mt Laurel, New Jersey, USA.*

[3]*Inspira Health Network Vineland, New Jersey, USA.*

***Correspondence:**

Jerome H. Check, M.D., Ph.D., 7447 Old York Road, Melrose Park, PA 19027, USA, Tel: 215-635-4400, FAX: 215-635-2304.

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ABSTRACT

Rationale: *A relative deficiency of dopamine in various tissues leading to increased tissue permeability allowing infiltration of irritants to cause inflammation with subsequent pain, or disrupt normal function of organs, may be the etiologic factor in a wide variety of medical conditions. Evidence to support this hypothesis has been shown by quick improvement of symptomatology after treatment with dopaminergic drugs especially dextroamphetamine sulfate, but also cabergoline, for both corporeal conditions and psychological ones.*

Objective: *To determine not only if treatment with dextroamphetamine may ameliorate backaches (which has been previously reported) but also improve chronic nightmare syndrome which has never been previously reported.*

Findings: *A total daily dosage of 18.8mg of dextroamphetamine sulfate was not only able to immediately completely relieve the backache, but while taking it he did not have one nightmare during three months of treatment. Previously he never had one week for 30 years without at least 1-3 nightmares.*

Conclusion: *Sometimes one case report provides more valid conclusions of the efficacy of a given drug than a randomized controlled study. The standard medication used for chronic nightmares is prazosin which may not be very effective in ameliorating chronic nightmares. The dramatic complete improvement of chronic nightmare syndrome, though it was only one patient, is sufficient for a treating physician to try dextroamphetamine therapy for prazosin failures or for patients who only had partial relief from prazosin and/or side effects, to try amphetamine therapy. Certainly, it would make sense to try dextroamphetamine for chronic nightmares if the patient also has other manifestations of the increased cellular permeability disorder.*

Keywords

Backache, Dopamine, Increased cellular permeability syndrome, Post-traumatic stress syndrome.

Introduction

Chronic nightmares develop through the interaction of elevated hyperarousal and impaired fear extinction [1]. This interplay may be facilitated by trait affect distress elicited by traumatic experiences, early childhood adversity, and trait susceptibility [1].

A meta-analysis comparing the efficacy of psychotherapeutics and pharmacological interventions for trauma-related nightmares in adults in 29 clinical trials involving 14 psychotherapeutic and pharmacologic interventions in 2214 trauma survivors concluded that psychotherapy had efficacy for treating nightmares with image rehearsal therapy and also the pharmacological use of the alpha blocker prazosin [2].

The American Academy of Sleep Medicine Task Force listed imagery rehearsal therapy as the recommended treatment for trauma-related nightmares and changed the recommendation of prazosin to "may be used." According to Vu et al. this

recommendation down grading the recommendation of prazosin was premature because Vu et al. reached similar conclusions with their meta-analysis as did Zhang et al. showing moderate to marked efficacy of this drug prazosin and claimed the AASM task force recommendation was based on a single randomized controlled trial of prazosin that showed little beneficial effect over placebo [3]. Trials with other pharmacologic interventions such as risperidone, and paroxetine did not prove beneficial [2]. Frequently with trauma a person may not only be left with chronic nightmares but also chronic physical pain from injuries. One 45-year-old marine had a history of severe trauma with bone fractures while serving in the Gulf War in 1993 with an improvised explosive devise leaving him racked in pain, which was not abated for 25 years despite 5 surgical procedures and the use of high dosages of oxycontin, oxycodone, and fentanyl. He had almost 100% relief after treatment with dextroamphetamine sulfate given as amphetamine tablets in a very short period of time and he was quickly able to completely stop all narcotics. The pain relief persisted over ten years while taking just amphetamine salts [4]. His worst pain was in his neck and lower back. The treatment with this dopaminergic drug also markedly improved his severe restless legs syndrome and chronic fatigue [4]. Dextroamphetamine sulfate has been reported to very effectively treat chronic fatigue [5-7].

Head trauma can lead to chronic severe headaches, which may be relieved very quickly after taking dextroamphetamine sulfate as seen in a 22 male suffering with severe headaches present almost the entire day related to 7 concussions while playing college ice hockey [4]. Even more impressive was a 20-year-old male who had severe constant daily headaches every minute of the day following 17 brain surgeries for a choroid plexus papilloma. Not only did he respond extremely well to dextroamphetamine sulfate, but the complete relief occurred within the first two hours of him taking the pill and the pain relief persisted for eight years only returning if he temporarily runs out of his medication. He had been refractory to all other medications given for relief of headaches [4].

Head trauma and concussion can lead to months or years of confusion and inability to think clearly. Two female high school students had severe headaches and confusion following a school bus accident requiring them to be home schooled for 6 months when one of them sought our opinion on some other therapy since various drugs prescribed by her neurologist failed to improve her severe headaches nor her state of confusion. She also stated that she developed de novo such severe stuttering that she could barely talk. All her symptoms, including the stuttering, were ameliorated within the first day of treatment with dextroamphetamine, another teenage girl seeing her improvement sitting in the same row in the bus, with exactly the same symptoms, made an appointment. Her symptoms completely disappeared in one day also [8].

Dextroamphetamine sulfate is well known to treat attention deficit hyperactivity disorder (ADHD) or just ADD and depression. We have also found it to be very effective for depression even when standard anti-depressants never proved not to be effective [9].

We have seen several unreported cases of chronic backache related to injuries relieved by dextroamphetamine e.g., a policeman whose back was broken by being hit repeatedly with a plank while trying to arrest a criminal. Dextroamphetamine has also provided marked relief for backaches even when there was no apparent injury involved in the etiology [10,11]. Thus, when a 51-year- old male wanted to be evaluated for severe backache, post-traumatic stress syndrome, and chronic nightmare disorders following a traumatic event, we assumed that they all occurred from a terrifying injury. Having experience with successfully treating backaches with dextroamphetamine, we agreed to accept his case.

Case Report

The lead author saw the patient in consultation for his main complaint of backache. He was referred by a friend who we treated for lower backache and who responded very well to treatment with dextroamphetamine sulfate. Patients generally fill out a complete history form prior to the visit and his history mentioned chronic nightmares as part of post-traumatic stress syndrome. The lead author assumed that both the backaches and the nightmares probably stemmed from the same event.

The lead author was surprised that the chronic backaches had been insidious with no traumatic events to consider as an etiologic factor. However, the chronic nightmares had been present for almost 30 years. They did begin right after a traumatic event, but it was the witnessing of the event that initiated these nightmares shortly after the traumatic event happened. He was stationed in Yuma, Arizona. He and some of his marine friends were on leave and they drove to Mexico in two cars. The car that he was not in flipped over and all of the passengers died. He extricated his best friend from the car who subsequently died in his arms. The patient was the duty sergeant and he had to be the one to inform all of the parents.

All non-steroidal anti-inflammatory drugs gave him gastrointestinal side effects and he stopped taking acetaminophen because of chronic kidney disease with a mildly elevated serum creatinine.

He had seen psychiatrists from several veteran administration hospital clinics, but no psychotherapies relieved the nightmares. He was never given any medication for the purpose of reversing the chronic nightmares. The nightmares occurred one to three times per week, and always involved either reliving the event of holding his dying friend in his arms or the strong emotional trauma he witnessed when he informed his friend's parents of the tragedy. For the 30 years there had never been one week without a nightmare. He also complained that he had a chronic problem mentally in focusing consistent with attention deficit disorder (ADD).

He was given 15mg amphetamine salts (9.4mg dextroamphetamine sulfate) upon arising and at noon. When he returned in three months his back pain was completely dissipated, and his ADD was much improved. He also stated that he did not have one nightmare since he started the amphetamines.

Discussion

There is a very large number of chronic disorders that are refractory to standard therapies but respond quite well to dextroamphetamine sulfate. They generally return if one stops the drugs but go into remission with the resumption of the drug, thus proving Koch's postulate. This beneficial effect is found to extend to all organ systems e.g., skin (urticaria, eczema, discoid lupus erythematosus, pruritus without skin lesions, bullous pemphigoid), oral-pharyngeal (recurrent aphthous stomatitis, stomatodynia, angioedema of the tongue, pharyngeal constriction of the throat from anaphylaxis), neurological (headaches, diplopia, mitochondrial lactic acid stroke-like syndrome, hereditary spastic paraplegia, multiple sclerosis, Parkinson's disease, intracranial hypertension, post-herpetic neuralgia, chronic complex regional pain syndrome –reflex sympathetic dystrophy), eyes (keratoconus and retro orbital stubbing pain, sixth cranial nerve paresis and diplopia), ears (autoimmune hearing loss, Meniere's disease) nose (chronic sinusitis) throat (painful thyroiditis, chronic pharyngitis) breasts (mastalgia, gynecomastia) heart (atrial fibrillation, premature atrial and ventricular contractions, postural orthostatic tachycardia syndrome), liver (autoimmune hepatitis), pancreas (chronic pancreatitis), esophagus (achalasia) stomach (gastroparesis, unexplained mid-epigastric pain, unexplained vomiting, gastrocolic reflux) intestines (pseudo intestinal obstruction, ulcerative colitis, Crohn's disease, microscopic colitis, mesenteric sclerosis, pathological constipation), urinary bladder (interstitial cystitis, neurogenic bladder with incontinence) pelvis (chronic pelvic pain, backache, mittelschmerz, dysmenorrhea, vulvovaginitis, vulvodynia, vaginismus, endometriosis, adenomyosis), musculoskeletal system (rheumatoid arthritis, fibromyalgia, aromatase induced arthralgia syndrome, frozen-shoulder syndrome, carpel tunnel syndrome, chronic fatigue syndrome), kidney (orthostatic edema), reproductive (infertility and recurrent miscarriage), metabolic (unexplained weight gain), temperature regulation system (heat intolerance, vasomotor instability, pseudo-pheochromocytoma).

Our group has published case reports on practically every one of these aforementioned conditions. Each case was chosen demonstrating quick long lasting correction of the problem with treatment with dextroamphetamine. Most of these references are available in a summary article where we propose our hypothesis that all of these conditions are related to the need for survival of the fetus to create spiral arteries through autoimmune mechanisms that depend on progesterone blocking dopamine, a biogenic amine in which one of its functions is to decrease cellular permeability. By blocking dopamine, irritants infuse into the pelvic tissues thus increasing inflammatory cells, especially natural killer cells, which, in turn, helps to remove the thick walls of the uterine arteries to create some thin-walled vessels (spiral arteries) to allow nutrient exchange between mother and fetus [12].

Since many of these conditions may co-exist, we refer to the conglomeration of these pathological disorders as the increased cellular permeability syndrome [13]. Other case report descriptions that are not included in these last 2 references may be found in subsequent case reports [14-20].

The original choice for treating our first case of the increased cellular permeability syndrome treated with dextroamphetamine sulfate was based on trying to find a drug that released more dopamine from sympathetic nerve fibers that theoretically would inhibit irritants from infusing into the dermis causing chronic urticaria of seven-year duration, that was almost constant, and covered most of her body. She had failed to respond to any conventional therapies. We chose dextroamphetamine over levodopa because the former had a lot less side effects. Her condition was so severe that she contemplated suicide. Bromocriptine was not yet available on the pharmaceutical market. The urticaria completely resolved in a short period of time and she has remained in complete remission for 40 years (only to return, if she temporarily runs out of medication) [21].

Though dextroamphetamine is well tolerated by most patients, some have side effects that preclude its use altogether, or inhibits raising the dosage sufficiently to eradicate the condition adequately. Furthermore, though not one patient in 40 years has ever become addicted to amphetamines in the dosages prescribed, and no one has ever been hospitalized from a serious side effect or died in our practice, for some reason, dextroamphetamine is classified as a class II drug in the same category as oxycontin, oxycodone, and fentanyl. In some states, e.g., New Jersey, the state where our medical school is located, precludes a state resident to obtain a class # drug for off-label use even in a different state, yet, confusingly, allows New Jersey residents to obtain marijuana or magical psychedelic mushrooms without even consulting a physician. Thus, in some instances an alternative drug is needed to release more dopamine. Indeed, we have seen both severe chronic pelvic pain and headaches improve with cabergoline, a dopaminergic drug, approved for hyperprolactinemia, galactorrhea and prolactinoma (based on the fact that dopamine is the prolactin inhibitory factor) [22,23].

However, in our experience, dextroamphetamine is more efficacious than cabergoline for most of these chronic disorders. Nevertheless, the response to cabergoline helps support the concept of the central role of dopamine or relative lack of it that allows excessive absorption of irritants into various tissues causing inflammation and subsequent pain or dysfunction of a given tissue [13]. According to the theory, various factors are associated with the multiple conditions under the umbrella of the increased cellular permeability syndrome. The increased cellular permeability of certain tissues, may be genetic, may be related to or susceptibility of certain tissues to become more permeable in the presence of viral or bacterial infections, medications, or trauma [13].

In the patient reported, in the end, all psychological or psychiatric conditions are related to some imbalance of biogenic amines. The immediate complete eradication of nightmares that were present for 30 years with a dopaminergic drug suggests that dopamine deficiency in the brain may be an important factor in the etiology of nightmares. As physicians, scientists, nurses, and other healthcare

workers we are taught that the most credible treatment is one that has been proven to be effective by a well powered, properly designed, randomized controlled trial (RCT). However, as seen with RCTs for chronic nightmares, often RCTs reach different conclusions. This leads to a meta-analysis to find the proper answer, and a conclusion reached today by a given meta-analysis may change tomorrow when a new RCT reaches a different conclusion, as was found when one very large RCT did not find that prazosin was much more effective than a placebo which shifted the conclusions by a subsequent meta-analysis that influenced the AASM task force to down-grade the recommendation for prazosin as "may be used" thus leading to the main recommendation for psychotherapy with image rehearsal therapy as the most recommended therapy. Obviously, it would be preferable for a patient to take a pill without side effects e.g., dextroamphetamine, rather than have to take time for psychotherapy, not to mention expense.

Generally, case reports are considered to have the least scientific merit. Unfortunately, when experts are requested to write a summary of the state of the art in treating a given condition, they frequently will not include case report studies. Almost all meta-analyses exclude case reports. Thus, discussions on the efficacy of novel off-label therapies e.g. dopaminergic drugs for a very effective treatment for a potpourri of medical conditions, will generally remain obscure from treating physicians who are relying on expert reviews. Thus, if one sees a case report of a novel way of treating a condition, instead of waiting for a RCT which may never happen, one could try that novel treatment on a given patient who is suffering from a pathological entity, especially if there are no more treatment options available, or if this possibly effective therapy may be less harmful to a patient rather than the next available pharmaceutical option e.g., trying dextroamphetamine sulfate before very expensive potentially dangerous (cancer and serious infections) immunosuppressive drugs.

It would seem that some psychiatrists still favor prazosin as an effective drug for chronic nightmare disorders. Hopefully, this case report could help initiate an RCT comparing prazosin to dextroamphetamine. Alternatively, perhaps some treating psychiatrists would try dextroamphetamine sulfate for patients with chronic nightmares not responding to prazosin and publish a series with their experience with dextroamphetamines in prazosin failures, or those stopping prazosin because of headaches or other side effects.

In today's age it is difficult to attain appointments with a psychiatrist. Perhaps a family physician or internal medicine specialist reading this case report would consider treating a patient with chronic nightmares with amphetamines and then publish their case report as to whether it was beneficial or not.

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