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The first case demonstrating marked amelioration of severe restless legs syndrome following treatment with the dopamine agonist dextroamphetamine sulfate

Abstract

The standard treatment for Restless Legs Syndrome (RLS) are dopamine agonist drugs e.g., pramipexole and ropinirole. There are a great number of drugs that are not dopamine agonists that have proven effective for RLS. Nevertheless, as many as 65% of patients with RLS are non-pharmacological users either because they were not greatly effective or because of side effects or expense of the available medications. The main side effect of the 1st line dopamine agonists is augmentation where over time these drugs may considerably worsen the symptoms and signs of RLS which would have not occurred if they had remained untreated or used 2nd line drugs. A sympathomimetic amine dextroamphetamine sulfate has been successfully used to treat a large variety of seemingly unrelated conditions which include pain and adverse neurologic conditions. These conditions have been lumped under one general name for the condition called the increased cellular permeability syndrome. The tenets of the pathophysiology of this increased cellular permeability syndrome is that inflammation and functional organ and tissue disruption is related to the inability of the mucosal barrier to prevent infusion of unwanted elements into these tissues because of relative dopamine deficiency. One of the functions of dopamine is to decrease cellular permeability. A case is presented of a woman with very severe RLS which did not improve very well following treatment with ropinirole and was stopped because of marked somnolence from the drug. This 70-year-old woman not only showed marked improvement of her RLS with no augmentation over 10 years, but she also had improvement in some of her other co-morbidities despite using only a small dosage of the amphetamine because of restrictions set by her cardiologist.

If confirmed by larger studies, dextroamphetamine may become the drug of choice not only for severe treatment resistant RLS with other co-morbidities present likely to also respond to the amphetamine therapy, but even in milder cases. Dextroamphetamine does cause the release of dopamine from sympathetic nerve fibers so it is a dopamine agonist, but because it also increases the release of other biogenic amines e.g., norepinephrine a sympathomimetic amine may be a better term.

Keywords: Restless legs syndrome; Dopamine agonists; Augmentation; Increased cellular permeability syndrome; Dextroamphetamine.

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Introduction

Restless Legs Syndrome (RLS) is a sensorimotor disorder associated with unpleasant sensations which seems to be relieved by movement [1]. The condition is exacerbated by inactivity and it is more common at nighttime or while sleeping [1]. The main treatment has been traditionally dopamine agonists e.g., ropinirole, pramipexole, and rotigoline [2-4]. Sometimes anti-convulsants e.g., gabapentin and pregabalin are used [2-4]. Other therapies include iron (either oral or intravenous), benzodiazepines, and even opioids [4].

Yeh et al state "However, in clinical practice, treatment is sometimes limited due to incomplete response or side effects" [5]. Yeh et al further state accordingly, it is necessary for clinicians and researchers to be aware of other lesser-known treatment modalities for RLS [5]. Yeh et al state that dopamine antagonists are not a panacea for treatment of RLS related both to cost of these drugs and side effects [5]. One of the main side effects of dopamine antagonists is augmentation, which is a paradoxical response where, instead of improvement, the RLS gets worse [6]. Furthermore, the effectiveness may wane after 2-8 years [6].

Yeh et al state that related to insufficient efficacy and side effects of dopamine agonists that up to 65% of patients with RLS use non-pharmacologic therapy e.g., acupuncture, massage, and herbal medicine [5,7]. Yeh et al performed an extensive review of the treatment of RLS including case reports. They divided alternative pharmacologic therapy into different groups based on their mode of action. Clonidine was the only drug whose mechanism of action was reduction of adrenergic transmission [5]. Thus, the theoretical benefit of clonidine was to reduce a potential contributing factor to RLS and that is hyperadrenergicity. Dipyridamole is an adenosine transporter inhibitor and thus increases extracellular adenosine in the brain by inhibiting adenosine transporters. Double blind studies have shown treatment efficacy [8].

Iron deficiency in the brain is thought to cause hypoadenosinergic state with down regulation of adenosine A1 receptors which are responsible for the inhibiton or the release of glutamate. One theory is that RLS may be related to an increased presence of glutamate in the thalamus [9]. Thus, drugs that inhibit glutamate may theoretically control the symptoms and signs of RLS. Drugs in this category that have shown efficacy in treating RLS include perampanel, amantadine, and ketamine.

As mentioned, gabapentin and pregabalin, drugs in the anticonvulsant family, have shown efficacy for RLS. Other drugs in this family include carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid, and levetiracetam. The results of various studies using these drugs have been summarized by Yeh et al and references to the various studies were included [5]. Since RLS can be triggered by infection, which frequently is associated with various autoimmune diseases and the presence of inflammatory markers, immunosuppressants e.g., glucocorticoids, have been used for treatment with beneficial effects [10,11].

Other drugs reported to have efficacy include cannabinoids, and the anti-depressant bupropion. The muscle relaxants baclofen and orphena drine acetate and physostigmine (which is an anticholinesterase inhibitor) have shown some efficacy in treating RLS [12-21].

Iron deficiency leading to low iron levels in brain tissue has been shown to be an etiologic factor in RLS and is the reason for one of its treatments given that has improved RLS and that is replacement iron. Iron is absorbed from food from the jejunum [22]. Weinstock et al provided evidence that small intestinal bacterial overgrowth, probably by inhibiting iron absorption can be associated with RLS [23,24]. Weinstock found that a one-month treatment with the antibiotic rifaximin which is used to treat irritable bowel syndrome when it is thought that the cause may be the small intestinal bacterial overgrowth demonstrated efficacy in ameliorating symptoms of RLS. Weinstock et al found that 2/3 of patients with RLS had small intestinal bacterial overgrowth and the RLS did improve in this subgroup following a 1-month treatment course with rifaximin [24].

Onabotulinumtoxinia (botulinum toxin type A) has been found to help RLS [25-27]. However, the degree of clinical benefit and consideration of cost and potential risk of muscle weakness and sometimes life-threatening complications does not make this type of therapy as a high priority especially when there are other treatments that seem to be more effective, less costly, and less risky [28,29]. There has been one report of the Monoamineoxidase (MAO) inhibitor type B selegiline that interferes with dopamine reuptake at the synapse. Selegiline also seemed to improve RLS [30].

RLS is frequently not merely an isolated pathological condition but may be associated with many other co-morbidities [31]. Weinstock et al suggest that many of the co-morbidities have an autoimmune diathesis [31]. The purpose of discussing this case report that we are reporting is to show that another dopamine agonist that has never been studied or published as a case report, as a treatment for RLS, dextroamphetamine sulfate, was highly effective for a severe case of RLS that was not very responsive to ropinirole and was stopped because of the side effects. Interestingly, there are many case reports and some case series (but no randomized controlled trials), showing that dextroamphetamine can ameliorate a large variety of pathological conditions that were refractory to standard therapy.

Case report

A 70-year-old female sought help for RLS in both legs of a 10-year duration that severely inhibited her from having adequate sleep. The interruption of sleep was not only from RLS but severe nocturia.

Other co-morbidities besides nocturia included chronic fatigue, hypertension, hypothyroidism, pruritus of the skin without lesions, ocular migraines, gout, and backaches. Her medications included for her hypertension atenolol 150 mg per day, and lisinopril 40 mg/day, atorvastatin 80 mg/day for hyperlipidemic. For gout she took allopurinol 200 mg/day. She also ingested low dose aspirin 81 mg/day for coronary artery disease.

The bilateral leg movements from the nocturnal RLS were so severe that she would consistently rip her bed sheets requiring her to buy new sheets every week or two. She had been treated with ropinirole in 2005, 10 years before we first evaluated her in 2015. The dosage was slowly titrated up to 4mg/day, but she only found mild improvement of RLS with the major side effect of severe daytime somnolence. Thus, she stopped the medication. She did not know why her treating physician did not try another drug for the RLS until we evaluated her 10 years later.

She stated that she had RLS every night without fail. We usually start the amphetamine salts at 15 mg immediate release tablet am and noon providing a total of 18.8 mg per day of the main ingredient dextroamphetamine when we treat other con-

ditions. However, her cardiologist was concerned about cardiac risks because of the concomitant release of catecholamines e.g., norepinephrine from sympathetic nerve fibers. Thus, he stated he would only be comfortable with a total of 20 mg/day of amphetamine salts.

She was started on 10 mg upon arising and at noon immediate release of amphetamine salts providing 12.5 dextroamphetamine sulfate even though this dosage is lower than what our observation of the efficacy of other drugs for over 40 years [32]. Nevertheless, she had a marked improvement in her RLS after she was evaluated 1 month later. She had no more episodes involving her left leg and only had a few much less intense episodes per month involving her right leg. She did have complete relief of her ocular migraine headaches and marked improvement in her backaches and pruritus. She had only a mild improvement in her chronic fatigue, and very little improvement in her nocturia though we were confident that an increase in her dosage would ameliorate the nocturia and fatigue and perhaps provide complete resolution of the nocturia. However, her cardiologist thought that her improvement was sufficient and suggested not to risk possible cardiac adverse events by increasing the dosage. Thus, she chose to adhere to her cardiologist's opinion.

Her RLS remained improved but after 5 years with her new insurance not paying for the off-label use of amphetamine salts she decided to see if the RLS may be in remission. There were no withdrawal symptoms from sudden cessation of dextroamphetamine as is typical of patients suddenly stopping the drug without weaning even in higher dosages (at least in our experience). There were only 2 nights of RLS with her right leg during the 1st weeks of stopping the drug which were consistent with the degree of RLS while taking the 20mg amphetamine salts. In week 2 of cessation, the episodes occurred almost nightly involving both legs but not that severe. However, after 2 weeks the severe RLS syndrome returned to its previous severity.

During that time her backaches and ocular migraines returned after the 1st week of cessation. Though she was never officially diagnosed with attention deficit deficiency, she realized that the amphetamine was helping her to mentally focus because her mind "become foggy" and when she stopped, she realized that she did have the same "foggy" symptoms before amphetamines were prescribed.

Upon resuming the 20 mg dosage 1 month later, the RLS went into almost complete remission again, her backaches disappeared, and she developed once again improvement in mental clarity and her pruritus dissipated once again. Though in her previous evaluations every 3 months, she had stated no improvement in the nocturia, she noticed that it became worse during the 1-month cessation of the drug. Thus, she now states mild to moderate improvement in nocturia. The chronic fatigue was never improved or worsened over the years, but she stated that she would put up with the fatigue rather than have a possible risk of an adverse cardiac event if we increased the dosage. She states however, that the extreme somnolence she experienced with ropinirole was so unbearable that she would not have been able to continue that drug even if instead of only mild improvement of the RLS it was completely eradicated.

Discussion/Conclusion

There is the possibility that the basis of most chronic disorders is a defect in some tissues having increased cellular permeability with the pathological manifestation of related to unwanted elements infusing into these tissues either causing inflammation or organ dysfunction. This condition has been termed the increased cellular permeability syndrome [33]. Since dopamine is released by sympathetic nerve fibers, it has been hypothesized that there may be a polygenic inheritance of relative dopamine deficiency that may manifest early in life or not until some other event e.g., infection or trauma makes a certain tissue more susceptible to the consequences of increased cellular permeability with the sympathetic nervous system unable to release sufficient dopamine to correct the problem [34,35].

There are a myriad of case reports demonstrating marked improvement of chronic treatment refractory conditions responding very well to dopaminergic drugs, especially, but not limited to, dextroamphetamine. Many of these interesting and convincing cases have been summarized [36-38].

Dextroamphetamine had been reported to provide marked amelioration of the co-morbidities that were present in the patient described including backaches, chronic fatigue, nocturia, ocular migraines, generalized pruritus without skin lesions, and edema leading to weight gain [35-49].

The forerunner of dopaminergic therapy for RLS is levodopa/carbadopa (Sinemet). It is not surprising that the first treatment used for RLS was levodopa carbodopa [50-52]. The data from the studies of the efficacy of the dopamine agonist sinemet led to the development of "better" dopamine agonists with subsequent approval by the Food and Drug Administration (FDA) for pramipexole, ropinirole, and ratigotines. However, these 3 drugs have the main side effects of augmentation with a rate found for pramipexole of 8% per year [6]. Augmentation refers to the drug making the RLS worse with greater intensity, more frequent episodes, greater disturbance of sleep, development of RLS originally restricted to sleeping hours to daytime, and even spread from restriction to legs only to now include arms [6]. Also reported was an increase in impulse control disorders [6]. Another side effect of the standard dopamine agonists is daytime sleepiness [53-56].

For the patient described here it is not clear if the RLS progressed to its severe state related to the etiologic factor becoming worse or whether it was related to augmentation from the short course of ropinirole treatment. She clearly has had no augmentation over 10 years of treatment with dextroamphetamine, only marked improvement. Other than dry mouth there has been no side effects.

With an experience of over 40 years of treatment with dextroamphetamine for a large variety of conditions we have never observed augmentation in any of these other disorders including neurological disorders e.g., Parkinson's disease, hereditary spastic paraplegia, mitochondrial encephalopathy lactic acid stroke-like syndrome or multiple sclerosis (MELAS) or an interesting case of a 6th cranial nerve palsy following every organism causing diplopia [36,57-59]. Even an 89-year-old man suffering such severe post-herpetic neuralgia with no relief from high dose opioids, who requested hospice with quick death, had complete relief of his pain with 1 month of treatment with amphetamine salts, and pain relief continued for 5 years until his death while sleeping at age 94 [60]. Our clinical observation is that dextroamphetamine is generally well tolerated and less than 10% of those treated stop the drug because of side effects (which are usually anger issues, persistent insomnia though in most patients it is only transient, and persistent decrease in ap-

petite which is also usually transient in most cases).

The biggest obstacle to the highly successful treatment of a plethora of medical conditions including, but not limited to RLS, is a class II narcotic restriction, Yet, in our experience in the dosages used no one in over 40 years has become addicted to dextroamphetamine, and this means thousands of patients. Over the last several years there has been a great push to try not to use opioids because of their tremendous risk of addiction. In a recent review by 4 leading experts in RLS from very prestigious medical centers in the United States, including the Mayo Center for Sleep Medicine in Rochester, Minnesota, Emory University in Atlanta Georgia, Massachusetts General Hospital, Boston MA, and the neurology clinic at the Mayo Clinic Southwest Wisconsin in a recent publication stated that " evidence-based use of opioid therapy for the treatment of restless legs syndrome is solid, particularly for prolonged-release oxycodone-naloxone which is a combination prescription not available in the United States" [61,62]. Gossard and the 3 co-authors state "with carefully supervised use and appropriate counseling chronic opioid therapy is appropriate for select patients with restless legs syndrome" [61]. The select group of patients to whom they are referring are patients who have failed other pharmacologic agents.

With a much higher safety profile for dextroamphetamine, this case, responding so well with her RLS for a long time without augmentation, and with improvement of other co-morbidities makes a strong case for using dextroamphetamine vs opioids for severe treatment refractory cases of RLS, even though this appears to be the only case where it has been tried. Hopefully, this case will inspire RLS experts to evaluate the efficacy of dextroamphetamine in a randomized controlled trial vs placebo or a randomized comparison study against another agent to treat RLS. Such a study should also evaluate the efficacy of the 2 drugs is also alleviating symptoms of co-morbidities.

Though the narrative review of the treatment of RLS by Yeh et al was extremely extensive, they did not mention the use of the dopaminergic drug cabergoline either. We did find one study which evaluated the efficacy of cabergoline for RLS [52]. We have used cabergoline to treat certain conditions e.g., pelvic pain, headaches, carpal tunnel syndrome, and chronic fatigue for patients who could not tolerate dextroamphetamine, or more commonly in patients from certain USA states that preclude the use of class 2 drugs off-label for their citizens even if no other reasonable therapy exists, and have demonstrated efficacy [63-65]. Pelvic pain, headaches, and pain from carpel tunnel syndrome are not usually considered as dopamine deficiency disorders e.g., Parkinson's disease and RLS. The fact that some dopamine agonist drugs can help these disorders that have been reported to be considerably helped by dextroamphetamine and cabergoline helps to support the contention that the mechanism of actions of dextroamphetamine sulfate is through its stimulation of release of dopamine from sympathetic nerve fibers, rather than other sympathomimetic amines e.g., norepinephrine or epinephrine for these various seemingly unrelated disorders that frequently occur together which we refer to as the increased cellular permeability syndrome.

The absence of augmentation not just in this one patient with severe RLS but the large number of patients treated with dextroamphetamine sulfate for a large variety of pathological conditions from almost every organ system could lead to speculation that perhaps its release of other sympathomimetic amines may somehow negate the risk of augmentation. Interestingly as mentioned it is believed that clonidine may help RLS by reduction of adrenergic transmission. Yet dextroamphetamine releases more adrenergic biogenic amines. Possibly the release of norepinephrine and epinephrine counteract the somnolence seen with dopaminergic drugs [66].

It is hoped that especially in the era of trying to markedly limit the use of opioids for pain that governmental agencies will consider lifting the class II narcotic regulation for dextroamphetamine to allow this relatively safe well tolerated inexpensive drug to provide relief for suffering patients who do not have any other better options for therapy. Daytime sleepiness is one of the symptoms seen with RLS and sometimes dopamine agonists can cause daytime sleepiness as seen in this patient. Perhaps the reason why is much less likely to cause sleepiness is due to the fact besides releasing dopamine, it also releases norepinephrines and epinephrine which can lead to insomnia.

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