Article Type: Case Series
Volume 2, Issue 2

INTERNATIONAL JOURNAL OF CLINICAL & MEDICAL CASE STUDIES

Dopaminergic drugs for treating chronic rhinosinusitis developing as a post coronavirus disease (COVID) complication

Abstract

Chronic rhinosinusitis can exist with or without nasal polyps. Evidence supports that the pathophysiology may be related to an epithelial barrier dysfunction leading to infiltration of unwanted elements that stimulate an inflammatory response. There is evidence that many other chronic pathological conditions considered often as autoimmune disorders are similarly related to epithelial cell barrier dysfunction, and the term used is the increased cellular permeability syndrome. There is evidence that is supported by marked improvement of these conditions by dopaminergic drugs that relative dopamine deficiency plays an important role in the etiology of these disorders including chronic rhinosinusitis as evidenced by the fact that long term treatment refractory males with this condition (but without nasal polyps) quickly improved after treatment of their chronic rhinosinusitis with the dopaminergic drug dextroamphetamine sulfate in one male and lisdexamfetamine mesylate in the other. We believe these are the first 2 case reports of the use of dopaminergic drugs for this condition. It is hoped that these reports will stimulate clinicians e.g., ears nose and throat specialists or allergists to test dopaminergic drugs to determine if this therapy is only effective in a minority or majority of cases and hopefully, they will report their results. The efficacy and safety profile of dopaminergic drugs in treating rhinosinusitis with and without presence of nasal polyps could then help to determine where to interject this therapy into the standard paradigm of treatment that has been recommended after meeting of experts in the field with their published recommendations.

Keywords: Chronic rhinosinusitis; Dopaminergic drugs; Chronic fatigue; Headaches; Increased cellular permeability syndrome.

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Received: Jul 19, 2025
Accepted: Aug 14, 2025
Published Online: Aug 21, 2025
Journal: International Journal of Clinical & Medical Case Studies

Introduction

Chronic Rhinosinusitis (CRS) presents with inflammation of the sinuses and nasal cavity that is present for at least 3 months [1,2]. Clinically CRS is divided into 2 types! Patients with nasal polyps and patients without nasal polyps [1].

The precise etiology is unknown. However, many clinicians and researchers consider that compromised mucociliary dysfunction may partially explain the mechanisms [3]. However, another proposed etiology is referred to as the barrier-hypothesis [3]. This concept considers that the cause may be related to the chronic inflammation developing related to an alteration in the epithelial barrier that is no longer able to prelude damage from external potential detrimental factors e.g., pathogens (bacterial, viral, fungal), or environmental irritants, or allergens [4-7].

Thus, alternations in epithelial cells, e.g., basal cells, goblet cells, submucosal glandular cells and secretary cells in the nasal epithelial layer leading to inflammation seem to be at the root of the problem. There has been a theory proposed that most chronic disorders, especially, but not limited to chronic inflammatory conditions, are related to increased cellular permeability [8-11]. The hypothesis contends that the increased cellular permeability allows infiltration of irritants into the tissues which leads to inflammation which causes pain and other consequences of disruption of normal cellular functions by these pathogens and irritants [8-11].

A huge amount of research extending to the present has been dedicated to the development of methods to disrupt the various pathways leading to the final step of infiltration of white blood cells causing the inflammation especially with the development of monoclonal antibodies. Not only are these immunomodulatory methods expensive but can lead to the development of life-threatening infections or even cancer by the general suppression of immune factors. The oldest treatments for these chronic inflammatory, possibly autoimmune disorders, are glucocorticoids. However, the emphasis on targeting specific pathways leading to inflammation by monoclonal antibodies was imitated to find a less toxic therapy than glucocorticoids related to their extra risks besides infection and cancer e.g., osteoporosis, muscle damage, psychogenic effects, diabetes mellites, hypertension, and Cushing's syndrome.

The biogenic amine dopamine has been shown to diminish cellular permeability. Thus, medications that release more dopamine were considered as possible candidates for treating various inflammatory or allergic conditions more than 40 years ago [8,10]. Drugs that were considered for the clinical research for treatment resistant chronic disorders of various types were levodopa/carbidopa and dextroamphetamine sulfate. The dopaminergic drug bromocriptine was not quite on the pharmaceutical market when this research began. Related to side effects of levodopa/carbidopa e.g. nausea and tardive dyskinesia, the decision was made to use dextroamphetamine sulfate as the dopaminergic drug for clinical trials [8-11]. Dextroamphetamine sulfate stimulates the sympathetic nervous system to release more dopamine. However, dextroamphetamine also releases norepinephrine and epinephrine. The term sympathomimetic amines rather than dopaminergic drugs were used to describe the use of this amphetamine. Thus, possibly the first case report of fully correcting one of these chronic disorders using dextroamphetamine, which was published over 40 years ago, showed dramatic quick resolution of very severe treatment resistant chronic urticaria (and the term sympathetic amines were used to describe the type of drug [12]. Subsequently, with the demonstration that a dopaminergic drug that is not a sympathomimetic amine is also effective in ameliorating treatment refractory inflammatory conditions, the term sympathomimetic amine has been replaced by the use of the term dopaminergic drugs [13-15].

There has been a large number of different pathological disorders with various clinical manifestations that were resistant to conventional newer immunotherapies that have had marked clinical improvement following treatment with dopaminergic drugs and they have been recently summarized [9,10]. We report for the first time 2 cases of chronic rhinosinusitis that responded well to the dopaminergic drug dextroamphetamine sulfate and lisdexamfetamine mesylate.

Case 1

The patient age 55 had denied any chronic nasal pathology until he developed coronavirus disease (COVID) in December 2021. His symptoms were predominately fever, cough, and very severe nasal congestion. Though the fever and cough abated, he developed such severe nasal congestion that he could hardly breathe. Skull x-rays revealed very severe involvement of many of the sinus cavities.

He received no relief following treatment with guaifenesin, oral decongestants, oxymetazoline spray, nasal flushes with navage. He also had no relief following treatment with zithromycin. The severe symptoms did not abate for 3 months when he started on lisdexamfetamine 50mg per day. He saw relief within 1 week and he was completely free of the congestion by 1 month.

He continued the lisdexamfetamine mesylate for 1 year and was completely symptom free. He took no other medication during that time. He stopped the amphetamines in January 2023, and he has been asymptomatic for 2.5 years.

Case 2

Following his second episode of COVID, a 33-year-old man developed a chronic rhinosinusitis pathological condition. The main manifestation of the condition was a moderately severe headache that would last 24 hours and improve after taking naproxen. However, it would return in 2-3 days so that he would have about 10 headache days per month.

The headaches were considered to be caused by chronic rhinosinusitis following a nasoscope and CT scan prescribed by his ear, nose, and throat specialist. He was prescribed ampicillins/clavulanate potassium for 1 week which would prevent the headaches, but they would resume within 2 days of stopping the antibiotic.

The ENT specialist next tried doxycycline for 1-2 weeks, but each time he stopped it, the headaches resumed. He tried taking doxycycline 100 mg per day for 1 month and had no episodes while taking it but the headaches resumed upon stopping also.

He had moderately severe gastrointestinal side effect, so he decided not to use them again even though the antibiotic did reduce the headaches while taking it. Interestingly post COVID he also had the complication of weakness in his arms and legs, but these symptoms would recur once the antibiotic was stopped.

He was then referred to an allergist who found him allergic to dust mites. However, more of his symptoms improved following treatment with fexofenadine. He thus decided to just live with the symptoms. However, after 2 years of suffering he re-consulted the ENT specialist. A repeat CT scan showed significant worsening of chronic sinusitis. Surgery was thus recommended.

At the advice of his wife, who is a patient at our practice that we successfully treated for severe headaches with dopaminergic drugs, to get our opinion. He was started on amphetamine 15 mg immediate release tablets upon arising and at noon (producing a total of 18.8 mg of dextroamphetamine per day). From the first day he started the medication he has not had a headache and has complete relief of his fatigue in the arms and legs.

Discussion

It is not surprising that the chronic fatigue seen in case 2 markedly improved following treatment with dopaminergic drugs. One woman was so fatigued that she found it difficult to get out of bed to make it to the bedroom door 3 months after completing chemotherapy for breast cancer. Within 1 week of taking dextroamphetamine she was able to resume 5-mile power walks daily and 100 push-ups [16]. A study was performed in 50 women whose chief complaint was chronic fatigue. At the 6-month mark of treatment with dextroamphetamine sulfate they filled out a questionnaire indicating whether their fatigue was worse, stable but no improvement, mild, moderate, or marked improvement and 48 reported marked improvement

and 2 reported mild [17].

Interestingly, case 2 reported improvement in the fatigue following antibiotic treatment, but it resumed when stopping. A case was reported of a woman who received multiple courses of antibiotics including doxycycline for chronic fatigue that was attributed to Lyme's disease. It had not worked [18]. Similar to case 2, her treating physician wanted her to take another full month of antibiotics intravenously in the hospital. Instead, she was treated with dextroamphetamine and the fatigue markedly improved after a short time [18]. Though the increased cellular permeability syndrome seems to be more prevalent in females, males also can develop the problem consistent with a higher prevalence of autoimmune disorders is women vs men. Case 2 may be the first case report of a male with chronic fatigue responding to dopaminergic drugs (though we have seen that many men in our practice improve their fatigue with dopaminergic drugs, just not reported).

Infusion of unwanted elements into mitochondria is suspected as the cause of the fatigue and improvement with dopaminergic drugs related to dopamine diminishing cellular permeability, thus, impeding mitochondrial dysfunction [19]. The most dramatic case reported was a woman who was wheelchair ridden for 25 years related to the Mitochondrial Encephalopathy Lactic Acidosis Stroke-like syndrome (MELAS) who was able to restore normal walking and normal activities after a month of treatment with dextroamphetamine sulfate [20].

There have been many anecdotal reports of marked amelioration of severe standard treatment refractory headaches with dopaminergic drugs but mostly in women [21-28]. There are some cases reported in males using dopaminergic drugs for severe treatment refractory headache which occurred as a result of 7 concussions in a young male from playing college ice hockey. There was another young male who had constant headaches without relief every minute of his waking hours that failed to respond to any prior treatments that was the result of 17 brain surgical procedure for a choroid plexus papilloma tumor [9]. One hour after taking dextroamphetamine his headaches dissipated, and he remained in total remission as long as he was taking the dopaminergic drug. Interestingly, occasionally he ran out of the prescription so he would be off the medication for a couple of days and within hours the headaches would resume [9]. We believe that cases 1 and 2 reported here are the first reported causes showing efficacy of dopaminergic drugs for headaches related to chronic sinusitis in males or females. Whether this beneficial action only helps patients who develop headaches related to sinus inflammation only applies to cases occurring following COVID infection (long COVID), or applies to all cases of headaches related to chronic rhinosinusitis remains to be seen if we can recruit more cases or this report encourages clinicians with a practice with a larger number of chronic rhinosinusitis cases and hopefully they would report their results pro or con. Similarly, if dopaminergic drugs are found effective for chronic rhinosinusitis presenting with headaches and/or nasal congestion even not as a long COVID complication, it would be interesting if it is effective for the type with nasal polyps. Neither of the patients described here had nasal polyps.

A recent summary article by Hildenbrand et al published a simplified stepnire approach to the treatment of chronic rhinosinusitis [29]. They state that step 1, basic therapy-topical nasal steroids and nasal rinsing with saline solution. If not effective they suggest the option of short-term systemic steroids and antibiotics [29]. Step 2, if step 1 fails, is to perform endoscopic sinus surgery of revisions (extended surgery if necessary) [29]. If neither step 1 nor step 2 is successful, then step 3 is to consider biologics which include various drugs that interfere with the interleukin-4/interleukin-13 pathway which has been summarized by Bachert et al [29,30]. There are 3 drugs dupilumab, (anti-IL-4/IL-13, mepolizumab (anti-IL-5) and omalizumab (ant IqE) [30]. Other drugs and where they effect the type 2 inflammatory pathway are in the pharmaceutical/pipeline or are involved in clinical trials and they have been summarized also by Bachert et al [30].

According to Hildenbrand et al summarizing the European position paper/EUFOREA that biologics should only be used after sinus surgery has failed and that 3 of 5 other criteria have been met! 1) evidence of type 2 inflammation (eosinophilia in tissue and/or increased IqE in serum, 2) contradiction to systemic glucocorticoid therapy, 3) marked impaired quality of life, 4) marked impaired sense of smell, 5) comorbid bronchial asthma [29].

Since dopaminergic drugs work so well for most chronic inflammatory diseases and autoimmune conditions including headaches of various etiologies, it is likely that a larger series of treating chronic rhinosinusitis will respond to this treatment [9,10,14,21-28]. The question arises as to based on efficacy and relative lack of severe side effects and little if any long-term risks where in the 3-step treatment paradigm proposed by Hildenbrand et al should dopaminergic drugs be considered [30]? Recent concepts consider epithelial barrier dysfunction in the pathophysiology of chronic rhinosinusitis, which is consistent with the tenets of the "increased cellular permeability syndrome" [8,31,32]. There is evidence that autoimmunity plays a significant etiologic role in the development of chronic sinusitis with polyps [33].

The main concept of the increased cellular permeability syndrome is that it is an autoimmune condition with pain and inflammation and cellular functional disruption related to inhibitor to treatment toxic elements from infusing into unwanted tissues. Though the conditions can be isolated to just one organ, as with autoimmune disorders in general, it is not unusual to have a generalized permeability weakness in general different areas of the body leading to multiple morbidities in different locations of the body related to relative dopamine deficiency. Thus, dopaminergic drugs by restoring the proper epithelial barrier in multiple tissues of the body leads to amelioration of symptoms involving multiple organ systems. Thus, it would seem logical to use dopaminergic drugs as 1st line treatment if there are more manifestations of the syndrome not just chronic sinusitis e.g., the marked weakness in the arms and legs seen in case 2.

Perhaps topical nasal steroids and nasal rinsing with ecline or possibly the addition of antibiotics could be tried first for isolated chronic sinusitis. However, it would seem more reasonable to try dopaminergic drugs before trying step 2, i.e., endoscope sinus surgery [30]. Related to expense, risk of infection and even cancer from blocking key pathways to inflammation which can lead to insufficient immunosurveillance leading to these 2 aforementioned complications, it would make more sense to use dopaminergic drugs even before large studies are performed to corroborate. The outcome of these 2 cases which correct the cause of the inflammation rather than suppressing key cytokines and enzymes required for the immune response relative to the defect in mucosal barrier. Thus, our view would be to try dopaminergic drugs before biologics even if endo-

scopic sinus surgery was performed but the results were not sufficient.

Conclusion

Dextroamphetamine and lisdexamfetamine release other biogenic amines than dopamine e.g., norepinephrine. Thus, one cannot state for sure whether we should state that sympathomimetic amines or dopaminergic drugs should be the right term to be used for the type of treatment received by these 2 men with severe headaches from chronic sinusitis. We suspect that the correct term should be a dopaminergic drug since we have found that pure dopaminergic drugs e.g., cabergoline, can be effective for severe treatment resistance headaches [14]. Recently, related to a shortage of dextroamphetamine and restrictions related to its class II status, our practice had successfully treated patients who could no longer obtain dextroamphetamine with low dosages of levodopa/carbidopa with equal success (unreported as yet).

Chronic rhinosinusitis can be added to the long list of chronic pathological conditions that seem to respond quite well to dopaminergic drugs even if they are refractory to standard therapy. Case reports demonstrate that a therapy can work, but only a larger clinical study can determine if the treatment works only in a minority of cases or the majority. Hopefully, these 2 case reports will encourage clinicians with a larger population of patients with chronic rhinosinusitis to try dopaminergic drugs. Since neither of these 2 patients had nasal polyps, it will be especially important to see if dextroamphetamine or another dopaminergic drug is only effective in cases without nasal polyps, or will these drugs also help in cases with nasal polyps? If it is found that even cases of chronic rhinosinusitis with polyps can respond to dopaminergic drugs it will be interesting to see if a higher percentage of chronic rhinosinusitis responds to dopaminergic drugs if polyps are not present or are they equally as effective?.

Funding and conflict of interest: Authors have no funding sources and no conflicts of interest to declare.

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