

## The Use of Dopaminergic Drugs for Treating Cutaneous Discoid Lupus Erythematosus: A Case Study

Jerome H Check<sup>1,2\*</sup>, Brooke Neumann<sup>3</sup> and Diane L Check<sup>2</sup>

<sup>1</sup>Cooper Medical School of Rowan University Camden, NJ, USA.

<sup>2</sup>Cooper Institute for Reproductive Disorder, Mt Laurel, NJ, USA.

<sup>3</sup>Inspira Health Network Vineland, NJ, USA.

### \*Correspondence:

Jerome H. Check, MD, Ph.D, 7447 Old York Road, Melrose Park, PA 19027, TEL: 215-635-4156, FAX: 215-635-2304.

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### ABSTRACT

*There are many therapies to treat discoid lupus erythematosus (DLE) which provide mild to moderate beneficial effect. However, none of these suggested therapies are ideal, and thus research continues exploring the immunological pathways responsible for DLE hopefully leading to the development of monoclonal antibody therapy to disrupt a key pathway leading to the pathological state. New brand-named drugs are usually associated with a hefty price and frequently there are significant side effects. Thus, ideally it would be very beneficial to re-purpose an inexpensive generic drug already on the market that is effective with little side effects. One such drug for DLE already exists, e.g., the anti-malarial hydroxychloroquine which frequently can be moderately successful. Another potential drug fulfilling these ideals may be a dopaminergic drug, e.g., dextroamphetamine sulfate, normally used for attention-deficit hyperactivity disorder which has been used to successfully treat other skin disorders e.g., urticaria, eczema, and bullous pemphigoid. The hypothesized mechanism involves releasing more dopamine from sympathetic nerve fibers. Dopamine diminishes cellular permeability, thus, theoretically inhibiting absorption of irritating elements into the dermis, which sets off an immune cascade. The case of DLE presented did not respond to standard therapy for DLE, but had a 100% remission with dextroamphetamine sulfate, which has lasted one and a half years so far.*

### Keywords

Discoid lupus erythematosus, Dextroamphetamine sulfate, Increased cellular permeability syndrome, Cutaneous lupus erythematosus, Scalp discoid lupus erythematosus, Dopaminergic drugs.

### Introduction

Cutaneous lupus erythematosus (CLE) is an autoimmune inflammatory disorder [1]. This disease is characterized by hyper-photosensitive skin lesions that tend to be recurrent [1]. Though CLE may be part of the generalized autoimmune condition known as systemic lupus erythematosus, it frequently remains restricted to the skin. CLE may present with slightly different histopathologic lesions, which allows division into three types: acute, subacute, or chronic lupus erythematosus (CCLE), and this latter type accounts for 80% of the cases of CLE [2]. The majority of cases of CCLE are

predominantly present on the scalp or face and when it is limited to this location, it is referred to as discoid lupus erythematosus (DLE) [3].

DLE lesions are more apt to result in scarring with subsequent alopecia and hyper-pigmentation. Most dermatologists treat DLE with highly potent topical corticosteroids and sometimes inject corticosteroids directly into the lesions [4]. Hydroxychloroquine has also been used with some success [4]. It is not completely clear what is the mechanism by which hydroxychloroquine sometimes improves the condition, but there is some evidence to support it works by inhibiting endosomal toll-like receptors [4,5]. Another interesting treatment option for DLE is thalidomide or a thalidomide derivative lenalidomide [6]. The beneficial efforts of thalidomide had been attributed to inhibition of the cytokine tumor necrosis alpha [7]. If these therapies fail then some dermatologists/

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rheumatologists will treat them with systematic immune suppressants e.g., azathioprine, oral corticosteroids, cyclosporine, methotrexate, mofetil, and mycophenolate [4].

All the above therapies have some side effects with the most serious ones associated with systemic immunosuppressants e.g., higher risk of infection or even malignancy. Though many patients get significant improvement with these therapies, some do not respond at all, and some have mild, but incomplete, improvement. The case described here will introduce a novel effective treatment with a dopaminergic drug for treating standard treatment resistant DLE.

### Case Report

A 39-year-old woman sought help to mitigate her symptoms of urinary urgency, frequency, and nocturia that was suggested to be interstitial cystitis. She also complained about mittelschmerz that would last 24 hours, and was increasing in intensity over time, and chronic lower abdominal pain in the right side that increased in intensity premenstrually. A review of systems found that in the last year she had developed erythematous pruritic scalp lesions that were diagnosed by biopsy as DLE. She was treated first with topical corticosteroids which were ineffective. She was then prescribed oral corticosteroids which she stopped because of psychogenic side effects. Systemic immunosuppressants were then recommended, but she refused that therapy after potential risks were explained to her. These treatments and suggested therapies were provided by the dermatological group that made the DLE diagnosis.

We suggested that refractory interstitial cystitis and mittelschmerz may be related to increased cellular permeability of those tissues and that drugs that release more dopamine have helped interstitial cystitis and other types of pelvic pain [8-11].

Though we have never treated DLE before, we mentioned that the increased cellular permeability can be present in several areas of the body, and thus this increased cellular permeability syndrome can affect several different organ systems in the same person [12]. In fact, dopaminergic drugs had demonstrated efficacy in eradicating some chronic treatment refractory skin disorders [13,14]. Within one month of taking oral amphetamine salts 15 mg AM and noon (containing 18.8 mg dextroamphetamine sulfate), she showed significant improvement, not only in the symptoms of interstitial cystitis and pelvic pain, but also resulting in less scalp pruritus. Gradually raising the dosage to a total of 80 mg amphetamine salts (about 43.2 mg dextroamphetamine sulfate), all of her symptoms completely disappeared including complete resolution of the DLE lesions. She has not had a recurrence of DLE for one and half years while continuing her dextroamphetamine sulfate. She has no side effects from this type of dopaminergic therapy.

### Discussion

As mentioned, though there are many drugs available on the pharmaceutical market to treat DLE, there are no FDA approved drugs. Currently, there is research investigating the immune mechanism causing DLE. The hope is that understanding the role

played by various parts of both the humoral and cellular immune system e.g., B cells, and various types of T cells (CD 4 + T cells, CD8 +T cells), gamma-delta T cells, regulatory T cells, and other while blood cells (macrophages and dendritic cells), a specific key pathway will be identified that can lead to the development of monoclonal antibodies that can provide a more efficacious response. Of course, if an effective monoclonal antibody is developed, based on research and development, and has required the steps in order to gain pharmaceutical approval, it will require over a billion dollars for the drug to get to market. Thus, when approval is granted, the drug will likely be inaccessible to most patients because of the cost and, perhaps, even if the patient has insurance coverage. This drives an increase in the cost of healthcare and the amount a person must spend to have a good health care plan. Not from our own clinical experience, but from reading the literature, the re-purposing of anti-malarial drugs e.g., hydroxychloroquine, may be a reasonable choice for treating DLE in that it is inexpensive, generally well tolerated, and at least some studies suggest that an improvement to some degree may be expected in about 50% of the patients treated [4]. We are not sure why hydroxychloroquine was not offered to this patient before advising immunosuppressants [4].

Dextroamphetamine sulfate is inexpensive, generally well tolerated, and not associated with long term side effects. In the dosages used, it is non-addicting allowing abrupt stoppage without withdrawal symptoms. We have been using dextroamphetamine sulfate extensively for a variety of medical conditions for over 40 years and there has not been one serious adverse event that has occurred. In fact, our first case report showing benefits of dextroamphetamine sulfate for a chronic treatment refractory condition was published in a dermatologic journal [15]. One of the cases had seven years of urticaria covering most of her body on almost a daily basis. Though not responding to any standard therapy, her urticarial lesions were completely resolved within one week of taking dextroamphetamine sulfate which she continued for 25 years. She failed to receive one month's supply of the drug, so she decided to see if she still needed it. Within a few days she was covered in hives once again which remained for one month until she re-started the medication. The urticaria completely disappeared within one week and has never returned while continuing dextroamphetamine sulfate for the last 15 years. The aforementioned case of eczema that cleared up quickly following treatment with dextroamphetamine had been present for over 20 years [14]. Recently a case of treatment resistant bullous pemphigoid quickly had a 100% remission following dextroamphetamine sulfate (unpublished as of yet but submitted).

Though the exact mechanisms of how hydroxychloroquine improves DLE is not known, Kuznik et al. hypothesized that it inhibits antigen processing and presentation by dendritic cells. Furthermore, the anti-malarial drugs may mask stimulating DNA epitopes preventing their recognition by endosomal TLR9 which leads to a decrease in interferon gamma production [5]. In contrast, we purposely sought to evaluate the efficacy of dopaminergic design to release more dopamine from sympathetic nerve fibers in view of our studies of fetal-implantation with evidence supporting

the creation of an increase in cellular immune response needed during the luteal phase to help convert some thick walled uterine arteries into thin walled spiral arteries to allow nutrient exchange between mother and fetus, was at least, in part, through progesterone inhibiting dopamine. This blockage of dopamine then allows an increase in cellular permeability, leading to normal absorption of irritating elements increased inflammation in fertile women, and excessive inflammation, associated with various types of pelvic pain, in infertile women or women with recurrent miscarriages. Indirect proof of dopaminergic drugs reducing inflammation was shown by a marked improvement in pelvic pain following treatment with these drugs in the case described here. Other factors in the dermis, possibly genetic, could lead to various types of skin lesions from urticaria, to eczema to bullous pemphigoid to DLE. However, effective treatment may only require the treating physician to prescribe medication to inhibit the permeability defect thus precluding subsequent immune response. Unfortunately, our group does not have a high population of patients seeking help for dermatological problems. The main goal of this manuscript is to interest physicians, who see a fair number of cases of DLE, to evaluate dopaminergic drugs.

One possible study to evaluate the efficacy of dopaminergic drugs for SLE would be for a dermatologist to treat DLE with their favorite topical corticosteroid. For those not responding sufficiently to randomly assign them to oral hydroxychloroquine vs dextroamphetamine sulfate in a comparative randomized controlled case study with a cross-over for those not responding to either agent. If the dermatologist is not comfortable using a class II drug off label, then one could substitute the dopaminergic drug cabergoline instead of amphetamines.

### Statement of Ethics

Cooper Medical School of Rowan University does not require IRB approval for retrospective studies. Written informed consent was obtained from participants for publication of the details of their medical case.

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