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# Dopaminergic Drugs for the Successful Treatment of Bullous Pemphigoid (BP)

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## ABSTRACT

*The case presented here describes a novel treatment for bullous pemphigoid that was extremely effective in a 68-year-old woman with a history of multiple sclerosis who developed a severe case of histopathologically confirmed diagnosis of bullous pemphigoid involving her trunk, back, and upper thighs. The lesions developed despite her 1 ½ years of treatment with the immunosuppressive agent ocrelizumab prescribed to treat multiple sclerosis (MS). A well-known physician at a university medical center who diagnosed the BP prescribed tetracycline, but this showed no clinical benefit. She was treated with dextroamphetamine for the purpose of releasing more dopamine from sympathetic nerve endings. Dopamine is known to decrease cellular permeability, thus inhibiting hypothetical irritants from infusing into the skin causing this type of inflammatory response. She had been previously treated for over 30 years with dextroamphetamine, which completely stopped rapid progression of MS. She moved 1000 miles, and her neurologist switched her to ocrelizumab because of unfamiliarity with treating MS with dopaminergic drugs and prescribed her ocrelizumab. She had a total remission of her BP in one week. She has not had any more skin lesions now for over a year while on therapy. Since current medical treatments for BP are not very affective and with the knowledge that dextroamphetamine has previously demonstrated efficacy in ameliorating other severe treatment resistant skin disorders e.g., urticaria, eczema, and psoriasis, and mucous membrane disorders e.g., recurrent aphthous stomatitis, this off-label safe treatment should be considered for BP in treatment resistant cases.*

## Keywords

Bullous pemphigoid, Sympathomimetic amines, Dopamine, Increased cellular permeability syndrome, Multiple sclerosis.

## Introduction

Pemphigus and pemphigoid diseases are chronic autoantibody-mediated bullous disorders of the skin and sometimes mucous membranes. Though both the pemphigus family of diseases and the pemphigoid family of diseases have in common diffuse skin blisters, there are distinguishing characteristics [1]. The family of pemphigoid diseases are related to autoantibodies against structural proteins of the hemidesmosomes and are characterized by intense blisters or other lesions on the skin and mucus membrane [1]. The three most common forms of pemphigoid are bullous pemphigoid (BP), mucus membrane pemphigoid (MMP) and epidermolysis bullosa acquista (EBA). These pemphigoid subtypes cause subepidermal splitting of the epidermis. In contrast, the blisters are intraepidermal in pemphigus, and thus, the blisters in pemphigus are more tense [1].

BP is the most common type of pemphigoid. It is most common among people of advanced age. The disorder is relatively uncommon and may depend on geographical location [1]. In Germany, the incidence is about 250 patients per million people, but is still about two and a half times higher than the incidence of pemphigus [2]. BP may have an association with chronic and acute neurological disorders including multiple sclerosis, Parkinson's disease, dementia, and cerebral vascular accidents. This may be related to an autoimmune reaction to a common antigen found in the dermis and brain called BP antigen 1 [3,4].

Secondary inflammation is more typical of BP than the pemphigus subtype [1,4]. Thus, one of the original treatments was corticosteroids, either oral or topical [5]. Tetracycline has anti-inflammatory activity, suppresses neutrophil chemotaxis, and inhibits proinflammatory cytokines and proteases. Thus, tetracycline, in combination with nicotinamide, has been found to improve BP in some cases [6]. Severe cases may warrant immunosuppressant treatment besides glucocorticoids. Other immune suppressants that have been tried including azathioprine, chlorambucil, cyclophosphamide, methotrexate and mycophenolate mofetil [4]. Some cases may respond to rituximab [4]. There may be also some benefits with intravenous immunoglobulin therapy [4]. Unfortunately, all of the aforementioned immunosuppressant treatments for BP have significant side effects and potential serious long-term risks e.g., infection or even cancer. A case is presented in an elderly woman with long term multiple sclerosis whose moderately severe BP cleared by 100% in a very short time frame by treatment with a well-tolerated, inexpensive, dopaminergic drug, with little risk of any long-term side effects.

## Case Report

A 68-year-old woman presented with multiple blister-like lesions on her trunk, back, and upper thighs that was diagnosed, based on clinical presentation and histopathology of biopsied lesions by a major universal well-renowned dermatology department, as bullous pemphigoid (BP). Immunofluorescence evaluation of the biopsied lesions demonstrated both the third component of complement and IgG at the basement membrane zone.

The patient consulted our practice, which specializes in reproductive and medical endocrinology issues, certain chronic medical conditions (not necessarily endocrinology) and cancer, especially, but not limited to, immunological pathophysiology and certain types of immunotherapy, to see if we had any additional thoughts on the BP, since the tetracycline therapy did not abate any of the painful blisters during the two months of treatment. She was disappointed that after a repeat consult with that university dermatology center that they had no alternative suggestion for her treatment.

This woman originally consulted our own practice at age 35. She was diagnosed at age 33 with multiple sclerosis (MS). She was having frequent episodes despite glucocorticoid therapy by age 35, and she was confined to a wheelchair. She had heard that pregnancy can reduce frequency of MS attacks and that possibly keeping a woman on estrogen and progesterone (P), treatment regimen could similarly reduce the frequency of MS episodes. Instead, we informed her of our research, based on embryo implantation models, that many autoimmune conditions, e.g., MS, are related to increased cellular permeability leading to infiltration of irritating agents that cause inflammation and damage, which in her case is the myelin sheath [7,8]. We advised her that we had been accumulating evidence that treating various medical conditions with drugs that release dopamine from sympathetic nerve fibers can effectively treat many inflammatory chronic pathological conditions. Dopamine diminishes cellular permeability. We were waiting to publish our findings but wanted to wait for cases where there was little question about the treatment resulting in a definite beneficial effect. In fact, our first case report in 1984 was in a dermatological journal in which a woman with extensive chronic urticaria that was present almost daily for seven years found long lasting (now over 40 years) eradication of the urticaria with treatment with dextroamphetamine sulfate [9]. Based on this model, we hypothesized that treating certain of these autoimmune conditions by dopaminergic drugs may decrease the abnormal increase in cellular permeability and thus, provide significant palliation of certain treatment resistant conditions. The choices of dopaminergic drugs over 40 years ago, when we decided to test this hypothesis by treating people with potential etiologic factors causing pathological conditions related to increased cellular permeability, was levodopa and dextroamphetamine sulfate. Bromocriptine was still not approved yet, and was known as CB 154. We chose dextroamphetamine because it had much less potential side effects than that of levodopa .

Her starting dosage of amphetamine salts was 15mg immediate release tablet (containing 9.4mg dextroamphetamine sulfate) AM and noon for the first month, then 20mg AM and noon in month two and 30mg AM and noon in month three. When she returned for evaluation of therapy in three months, she stated that her fatigue was markedly improved. She never had another episode of MS in the 31 years that we treated her with dextroamphetamine sulfate. She moved from Pennsylvania, one thousand miles away, to Florida. She could not find one physician willing to continue with her off-label treatment with dextroamphetamine. Instead, a neurologist began treatment with ocrelizumab. She continued with no more MS attacks for the one and a half years on exclusive ocrelizumab. Over the years, she was able to improve from being wheelchair ridden to walking with the aid of a walker.

After one year and a half year off dextroamphetamine, and maintaining ocrelizumab, she developed BP. We advised her that even though we have never treated BP before, we have seen many long term skin disorders improve following treatment with dextroamphetamine sulfate including urticaria and eczema [10,11]. Even though her BP was confined to the dermis, we explained that sometime BP involves the mucosal membrane, and that we have seen marked improvement in very severe long term recurrent aphthous stomatitis very quickly following treatment with dopaminergic drugs [12]. She was restarted on 15 mg immediate release amphetamine salts (9.4 mg of dextroamphetamine) AM and noon. Her BP was completely eradicated in one week. It has remained in complete remission for over one year. She continues on both the dextroamphetamine sulfate and ocrelizumab, and she notes that her previous mild fatigue while on ocrelizumab alone, has also improved by the addition of this dopaminergic drug [13]. Written consent was obtained from the patient who is being reported to present this case. However, she preferred that pictures of her lesions, which were taken at the aforementioned university dermatology center, not be included.

## Discussion

With no prior experience in treating BP, we cannot comment

as to whether the recommended treatment with doxycycline without any other suggested therapy by a renowned university dermatology group was the best treatment option available, or if another expert in BP treatment would have considered an alternate therapy. Perhaps considering she was already on an immunosuppressive drug, the dermatology group was concerned that adding an additional immunosuppressive drug could lead to serious complications, or concern that stopping ocrelizumab, in favor of another immunosuppressant to try to help the BP, may not be the right drug for her MS, and thus may allow her MS to reoccur. This case does show that the combined use of dextroamphetamine sulfate and ocrelizumab seems to be a compatible regimen, at least in this one case.

Consistent with our model of embryo implantation, which suggests that progesterone blocks dopamine, and this allows irritants to infuse into pelvic tissues leading to increased natural killer cells and cytotoxic T cells in order to remove the thick walls of some of the uterine arteries to create thin-walled spiral arteries to allow nutrient exchange between mother and fetus, some conditions only occur premenstrually. Indeed, dopaminergic drugs have been shown to eradicate premenstrual urticaria and anaphylaxis [14]. It should be noted however, that conditions that are related to increased cellular permeability that respond to dopaminergic drugs are not restricted to women [15].

Hammers and Stanley, in their excellent review of BP, discuss the new therapeutic approaches in the pharmaceutical pipeline (4). Hopefully this case report and discussion will encourage the pharmaceutical companies to explore dopaminergic drugs for treatment of BP.

## Statement

The ethics committee of Cooper Medical School of Rowan University (formerly Robert Wood Johnson Medical School) and Inspira Health Network does not require IRB approval for an off-label use of a drug for a given individual if that drug was in the best interest of the patient, and the patient was aware that this was an off-label use. Those conditions were fulfilled for the subject of this case report. In fact, this was not a new drug for the patient, she had been on it for decades previously. It was merely restarted when she developed bullous pemphigoid. Written informed consent was obtained from the patient for the publication of this case report. There are no pictures included showing bullous pemphigoid by her request.

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