CASE REPORT

# Low Dose Naltrexone in Conjunction With the Wahls Protocol to Reduce the Frequency of Chronic Migraines in a Patient With Multiple Sclerosis: A Case Study

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**Abstract**

This case study investigates the efficacy of low dose naltrexone (LDN) and the Wahls Protocol in reducing the frequency and severity of chronic migraine headaches in a 62-year-old White female with multiple sclerosis. Migraines are common among the many debilitating symptoms of multiple sclerosis. A therapeutic intervention of low dose naltrexone titrated to 4.5 mg nightly in combination with dietary changes significantly improved the patient's quality of life by reducing the severity, duration, and frequency of her chronic migraine headaches.

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## Introduction

Multiple sclerosis (MS) is the most common demyelinating, chronic, inflammatory disease of the central nervous system (CNS).[1] MS courses of disease are either relapsing-remitting (RRMS) or primary and secondary progressive.[1,2] The secondary progressive course occurs after a patient has had a relapsing-remitting course that has progressed in disease activity.[1] Approximately 90% of patients with MS have the RRMS type when first diagnosed, while the remaining approximate 10% are diagnosed with the primary progressive form.[1] All forms of MS present with several symptoms and comorbidities, which are widely variable among patients.[2,3] These symptoms may include, but are not limited to weakness, Lhermitte sign (electric shock sensation in the neck), disturbances in gait, coordination and vision, tremors, fatigue, neuropathy, and depression.[3] Standard of care treatments for MS include use of monoclonal antibodies that target the CD20 antigen on B cells, which will rapidly deplete the number of B cells in the body, thereby reducing the attack of B cells on oligodendrocytes, and significantly slowing disease progression.[1] Treatment for MS relapses commonly include intravenous corticosteroids, physical therapy, and narcotics.[1]

Migraine pain is typically characterized as throbbing, is located either unilaterally or bilaterally in the temporal or occipital regions, and may or may not be preceded by aura.[4] Aura is defined as transient neurological symptoms, which occur prior to the onset of migraine pain, lasting from 5-60 minutes in duration.[4,5] Approximately 20% of patients with migraine pain experience aura prior to the onset of their pain.[4] These types of severe headaches are the most common recurrent types in at least 20% of women and 10% of men.[4] Migraines are most commonly accompanied by symptoms of nausea, vomiting, photophobia, phonophobia, anorexia, and vertigo.[4,5] In most patients, the typical symptoms experienced along with pain are nausea and/or vomiting, photophobia, and phonophobia.[4] Common migraine triggers include dehydration, food sensitivities, bright lights, loud noises, strong aromas, certain medications, alcohol, high stress, and some genetic variants.[4,6] The majority of migraine sufferers will have postdrome symptoms. These may or may not include a continued headache that feels as if their head is bruised, nausea, fatigue, and continued photophobia and phonophobia.[4] Although there are internal and external triggers, genetics play a major role in whether or not a person suffers from migraine headaches.[4] Many of these patients also have a tendency toward concomitant depression, anxiety, sleep apnea, postural orthostatic tachycardia syndrome, or chronic pain syndromes like fibromyalgia.[4] Migraine headaches are considered chronic when such symptoms are present for 15 days or more each month.[4] Standard of care treatments for migraine headaches include removal of recognizable triggers to help prevent occurrence, and first-line abortive treatments, such as over the counter non-steroidal anti-inflammatory drugs (NSAIDs) or triptan medications.[4,5]

**Timeline**
**Table 1**

| | Relevant Past Medical History |
|---|---|
| Prior to 02/2020 | MS diagnosis occurred in 2007. Patient's intractable migraine headaches began following MS diagnosis; episodes lasting 2-3 months in duration. |

**Table 2**

| Date | Visit Summary | Intervention |
|---|---|---|
| 2/1/20 | Initial visit:<br>• CC: Migraine Headaches-intractable to multiple treatments. | • LDN -1.5 mg qhs for one week; increase by 1.5 mg weekly to max dose of 4.5 mg qhs.<br>• Wahls Protocol recommended |
| 3/21/20 | Follow-up:<br>• Reports significant reduction in migraine h/a frequency, duration, and intensity. | • Continue 4.5 mg qhs<br>• Continue Wahls Protocol |
| 8/17/20 | Follow-up:<br>• Reports continued reduction in migraine h/a frequency, duration, and intensity.<br>• Reports improved sleep quality.<br>• Reports only one to two migraine h/a per month since last visit.<br>• Reports improved energy, mobility, and cognition.<br>• Reports temporary discontinuation of LDN for seven weeks. | • LDN-1.5 mg qhs for one week; increase by 1.5 mg weekly to max dose of 4.5 mg qhs. (reinitiated titration due to lapse in LDN use)<br>• Continue Wahls Protocol |
| 12/7/20 | Phone call:<br>• Reports continued reduction in migraine h/a frequency, duration, and intensity.<br>• Reports only one migraine episode since last visit.<br>• Reports significant increase in quality of life since tx initiation. | • Continue 4.5 mg qhs<br>• Continue Wahls Protocol |

**Abbreviations:** CC, chief complaint; LDN, low dose naltrexone; qhs, every night; h/a, headache; mg, milligram; tx, treatment.

## Presenting Concerns and Clinical Findings

A 62-year-old female with previously diagnosed RRMS initially presented to clinic seeking adjunctive treatment for her chronic, debilitating, intractable migraines without aura. She reports her migraines have been present since 2006 when she was diagnosed with MS. Her first brain magnetic resonance imaging (MRI) in 2006 showed "non-specified white matter of right parietal lobe, suggestive of demyelinating process." This MRI and subsequent computed tomography (CT) of the head had ruled out structural causes of migraine headache aside from demyelination. Imaging has occurred annually since 2011, exhibiting stability of disease. The patient reported migraine episodes that lasted from 30 to 90 days in duration, approximately equating to 50%-70% of the month and 60% of the year. Her migraine pain typically began as sharp "like rusty nails" and right-sided, which progressed to the eyes, jaw, and parietal regions, and felt "like a vice." The severity of her symptoms ranged from 6-10/10 (10 worst). She reported concomitant symptoms of nausea, vomiting, anorexia, blurred vision, photophobia, and phonophobia during these episodes. Her headache triggers included increased stress, dehydration, and consumption of red wine and chocolate cake. The patient also suffered from many MS-related symptoms, including depression, insomnia, neuropathy, and impairments in gait, coordination, and cognition.

The patient was diagnosed with osteoporosis by dual energy x-ray absorptiometry (DEXA) scan after a fall in June of 2020. Her past medical history is also significant for herpes zoster. Her family history of neurological conditions is unknown.

The patient's current medications include alendronate (Fosamax) 70 mg weekly, venlafaxine (Effexor) 250 mg daily, and vitamin D3 (2000 IU daily). For migraine treatment, she had previously tried multiple onabotulinumtoxinA (Botox) injections, divalproex (Depakote) 250 mg, ketorolac (Toradol) injections,

galcanezumab-gnlm (Emgality), and supplementation with Butterbur (*Petasites hybridus*) and magnesium, all of which had little to no symptom benefit.

## Diagnostic Assessment

The diagnosis of MS is largely dependent on medical history and the presence of neurological deficits[7]; such deficits must be localized, present for at least 24 hours and not due to infection.[7] There are no laboratory (lab) tests specific to MS, however a complete blood count (CBC), complete metabolic panel (CMP), thyroid panel, lipid panel, viral serology, and antinuclear antibodies (ANA) are typically investigated to exclude other causes of neurological deficits.[7] A diagnosis of MS can be confirmed with magnetic resonance imaging (MRI), demonstrating dissemination in time and space in localized areas of the central nervous system.[7] A lumbar puncture (LP) to analyze the cerebrospinal fluid can confirm a diagnosis.[7]

The prognosis of MS is dependent on age of onset, the treatments utilized, and the degree of disease progression.[8] Untreated patients have a 30% chance of developing physical disabilities that will significantly impact their lives within 20-25 years following symptom onset.[8] MS can shorten life expectancy minimally, with patients typically passing from secondary complications.[8]

Migraines are diagnosed clinically based upon the patient's reported symptoms, and symptom severity, duration, and quality.[4] The duration of migraine headaches is typically between 4-72 hours; however, episodes may last up to several months at a time.[4] There are currently no lab tests or imaging that can definitively diagnose migraines, but MRI or computed tomography (CT) scans are often used to rule out more concerning acute pathologies such as stroke, space-occupying lesions, and temporal arteritis.

The prognosis of chronic migraine headaches is good if the patient receives appropriate treatment to control the symptoms and prevent future migraines.[9] Medication overuse and lack of treatment adherence are indicators for a poor prognosis.[9]

This patient presented to clinic with an existing RRMS diagnosis and is managed by a neurologist. The diagnosis was confirmed by a brain MRI showing evidence of demyelinating disease prior to her office visit at The National University of Natural Medicine Health Center. Her migraines were recurrent, with episodes lasting longer than 72 hours, occurring greater than 15 days per month, for more than 3 consecutive months, and are by definition, chronic.

## Therapeutic Intervention

Naltrexone is an opioid antagonist that is typically used to treat drug and alcohol addiction, at oral doses of 25-50 mg or 380 mg intramuscularly.[12] Low dose naltrexone (LDN) at doses of 5 mg and lower are used for the treatment of several chronic pain syndromes.[11] LDN has been demonstrated to reduce pain and depression, improve physical function, and increase quality of life.[11] Both chronic pain syndromes and autoimmune conditions have been associated with elevated levels of inflammatory markers, which may explain the symptoms associated with these conditions. LDN acts as an antagonist on Toll-like receptor 4 (TLR-4) and modulates glial cells, which downregulate cytokines, thereby reducing inflammation and associated pain.[12]

The use and mechanism of action of naltrexone can be explained by the 'hormetic principle,' which asserts that certain pharmacological or toxic agents differ in their effects on the human body by the amount of these agents in the human system.[12] This helps to explain how higher doses of naltrexone can be used to assist in drug and alcohol addiction as an opioid antagonist, while at low doses, it is a glial modulator, assisting in the reduction of inflammation.

A titration schedule of LDN should be utilized to minimize possible disturbances in sleep as well as any gastrointestinal side effects. Insomnia and/or vivid dreams have been reported as disturbances with sleep.[12] Nausea, cramping, vomiting, and/or diarrhea have been reported as the common side effects in the gastrointestinal system.[10] The patient followed the titration schedule of 1.5 mg nightly for the first week, 3 mg nightly for the second week, then 4.5 mg nightly, thereafter. Minimal vivid dreams were reported by her; however, they did not cause enough disturbance to warrant her ceasing the medication.

The Wahls Protocol is a dietary regimen created by Terry Wahls in 2008, based upon her research of the many health effects of modifiable lifestyle measures through her research into functional medicine.[13] Much of Dr. Wahls' research began after her own diagnosis of RRMS. After 3 short years, Dr. Wahls had begun chemotherapy to slow the disease progression of her MS.[14] While searching for ways to avoid complete disability, she discovered research on various supplements that could potentially slow her disease progression.[14] She extrapolated food sources from the extensive supplement list as a way to simplify the process and make it more affordable.[14] From this discovery came the Wahls Protocol. This protocol has been studied extensively in patients with MS and other autoimmune conditions, not only by Dr. Wahls, but many other researchers. Rheumatoid arthritis and MS are the two most studied conditions to have received significant benefit from this protocol.

This diet emphasizes the consumption of a minimum of 9 cups of fruits and vegetables per day, with the addition of one serving each of seaweed, algae, and nutritional yeast, 12 ounces of lean organic grass-fed organ meats per week, and 16 ounces of fish per week. In addition, the elimination of gluten, grains, legumes, eggs, dairy, and nightshade vegetables is recommended due to the potential for these foods to contribute to inflammation in persons that may already have elevated inflammatory markers

such as those with autoimmune disorders, thus worsening symptoms.[13] Nightshade vegetables have been shown to upregulate the autoantibodies causing excess disease activity in autoimmune disorders.[13] This is due to their lectin and alkaloid content, possibly reacting with and increasing activity of autoantibodies.[13] Lectins are also associated with damage to the intestinal wall, allowing for permeability,[13] which allows bacteria, fragments of food, and other inflammatory substances to leak into the bloodstream, upregulating the immune system. For persons with autoimmune disorders, upregulation of the immune system can cause excess damage to healthy cells in the brain, nerves, muscles, and integumentary system.[13] The Wahls Protocol is rich in flavonoids and other antioxidants as well, which have been demonstrated to reduce inflammation by downregulating cytokines and reducing the formation of free radicals.[13]

## Follow-up and Outcomes

At her one-month follow-up visit she was encouraged to continue the Wahls Protocol, as long as she continued to note symptom improvement; she had endorsed decreases in the frequency, severity and duration of her migraine headaches, as well as improved sleep. She also reported instances of migraine headaches with increased intensity and duration during the 7-week lapse of LDN use, and when she deviated from the dietary protocol.

The patient has remained compliant with LDN and the Wahls Protocol through present day, with continuous use for the past 11 months, with the exception of a 7-week lapse in LDN use, due to a temporary change in evening routine. She reported that her quality of life has significantly improved, and her migraine headaches have reduced to a total of 3 episodes, each episode lasting 2-3 days, since treatment initiation. She also reported reductions in pain severity, improvements in fatigue, sleep and mood, and increased physical mobility. Her only reported side effect was vivid dreams, which did not disturb her sleep nor cause her to discontinue the protocol. She reported noticing benefit from the combination treatments beginning approximately 6 weeks following initiation.

## Discussion

The strengths of this case were the patient's significant symptom improvement and adherence to the recommended treatment protocols. Along with the significant reduction in migraines, the patient had significant improvement in depression, insomnia, neuropathy, impairments in gait, coordination, and cognition. A limitation of this case was the simultaneous initiation of LDN and the Wahls Protocol, making it difficult to identify the specific source of her significant symptom improvement, which could be due to the reduction in inflammation from LDN or the removal of inflammatory foods while adhering to the Wahls Protocol, the increase in antioxidant-rich foods, or the combination of these factors. Another limitation is that the Wahls Protocol can be difficult to maintain for long periods of time due to its restrictive nature and its demands related to supply sourcing and preparation. Future considerations should include a trial of a less restrictive diet, initiation of either LDN or dietary protocols instead of both at the same time so as to be able to clearly see which treatment option reduces patient symptoms the most. If the reduction of symptoms does not occur when utilizing only one of the treatments, further research should be done with the combination of LDN and an anti-inflammatory dietary protocol.

Although the patient reported that she did not suffer from migraine headaches until after her MS diagnosis in 2006, it is difficult to know whether the patient's migraines are a symptom of MS or a separately occurring disorder. The marked reduction in her migraine symptoms with the aforementioned protocols warrants further investigation in patients with similar symptoms. The use of one or both of these treatment protocols should be considered in the future in patients with MS and/or chronic migraine headaches.

## Patient Perspective

The patient was ecstatic that after many years of suffering from severely debilitating, long-lasting migraine headaches without previous relief, she found the recommended protocols to be "life changing." She also reports that her neurologist is "very happy" with the results of these treatments and encouraged her to continue them.

### Ethical Considerations

The authors declare no conflicts of interest in this case.

HIPAA Privacy Rule [45 CFR 164.501, 164.508, 164.512(i)]

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