

# Transdermal Histamine in Multiple Sclerosis: Part One – Clinical Experience

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## Abstract

Histamine has a long history of therapeutic use in many diseases, including multiple sclerosis (MS). Recently, transdermal histamine has been successfully employed for the amelioration of symptoms of both relapsing-remitting and progressive multiple sclerosis. This paper summarizes preliminary experiences with transdermal histamine for MS at the Tahoma Clinic: 67 percent of 55 patients using histamine transdermal cream had improvements in one or more areas, including extremity strength, balance, bladder control, fatigue, activities of daily living, and cognitive functioning, sustained for periods of up to three months. One-third of patients had improvements in three or more areas of functioning. Five possible mechanisms of action are postulated: augmentation of subnormal cerebral tissue levels of histamine; improved electrical function of demyelinated fibers; increased cerebral blood flow; suppression of autoimmune responses; and stimulation of remyelination. These will be discussed in detail in Part 2 of this article.

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## Introduction

Research directed toward the development of new treatments for MS is ongoing, but the current therapeutic mainstays include interferon and glatiramer acetate. These therapies all have a significant number of side-effects, are poorly tolerated by a substantial number of patients, and do not improve level of function, although they may slow disease progression. Glucocorticoids, employed in acute MS or relapse, may improve level of functioning but have serious long-term side-effects.

Histamine has a long, if not widely publicized, history as a therapeutic agent. In 1944, Bayard T. Horton, MD, of the Mayo Clinic wrote about his 17 years of clinical usage of histamine in a wide variety of settings.<sup>1,2</sup> Histamine therapy is still employed by otolaryngologists today for a number of disorders, including Bell's palsy, vasculitis, Meniere's disease, and other vestibular disturbances.<sup>3</sup> Almost 50 years ago, Hinton Jonez, MD, of Tacoma, Washington treated over 1500 MS patients by means of slow intravenous infusions of histamine.<sup>4</sup> He estimated that by 1952 he had administered approximately 150,000 such treatments without incident. Jonez

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was building on the earlier work of Horton, who reported improvements in 60 percent of 102 patients with acute and chronic MS.<sup>1,2</sup>

Recently, histamine has once again been employed effectively for the relief of symptoms and signs of MS. A proprietary transdermal histamine cream has been administered to over 800 patients across the United States, with anecdotal reports of improvement in 80 percent of users.<sup>5</sup> At the Tahoma Clinic in Kent, Washington, the therapy has been shown to be effective in 67 percent of cases. Thirty-four percent of a group of 55 users experienced significant improvement in three or more areas of functioning as defined by visual analog scales, while 33 percent saw improvement in one or two areas of functioning. The therapy is well tolerated by most individuals.

The study is ongoing; at the time of this writing a small number of patients using transdermal histamine cream have been followed for periods of up to eight months with sustained benefits.<sup>5</sup> The originator of the transdermal therapy, also an MS sufferer, continues to receive benefit after three years of continuous use. At first glance, the effect of transdermal histamine in MS appears to be an unexpected and improbable finding. Nevertheless, the observed clinical improvements are, in some cases, so striking it is the belief of the authors this therapy should be studied intensively in controlled trials.

### Clinical Experience with Transdermal Histamine at the Tahoma Clinic

Histamine transdermal cream was prescribed for 55 consecutive patients with MS without regard to disease classification or time elapsed from formal diagnosis. The sex/disease classification stratification of the patient population is summarized in Table 1. All patients had a neurologist-confirmed diagnosis of MS, in some cases including MRI, lumbar puncture, and evoked potentials. The subjects range in age from 30-77 years.

The cream consists of a proprietary mixture of histamine and caffeine. After application (usually to the anterior thigh), the site was occluded with an air-tight adhesive patch. Two consecutive patches were applied daily, each worn for eight hours for a total of 16 hours daily.

Patients taking the spasmolytics Baclofen or tizanidine hydrochloride (also known as Zanaflex®) were asked to taper their dosage and/or eliminate these medications within the first two weeks of starting the cream, if possible. Patients on interferon or glatiramer acetate continued these medications. All patients were counselled to avoid histamine (H1 or H2) blocking medications.

Prior to starting treatment, patients were asked to rate their symptoms in a number

**Table 1: Stratification of Patients Receiving Histamine Transdermal Cream**

Sex	Relapsing/ Remitting	Primary Progressive	Secondary Progressive	Classification Unclear
Male	3	8	8	1
Female	9	16	8	2

of areas, such as weakness of extremities, balance, walking ability, visual symptoms, and urinary control, using visual analog scales (VAS). Prior to six-week follow-up, patients were again asked to rate their symptoms using the same instruments. A copy of the questionnaire is available from the principal author on request.

Patient self-reporting of symptoms is an accepted technique for MS. Gulick demonstrated significant agreement between patient self-ratings of Activities of Daily Living and neurologist-determined disability scores, and consistency between patient self-reporting of symptoms and neurological exam.<sup>6</sup>

A score of 10 on the VAS for a given symptom denoted the worst imaginable severity for that symptom, whereas a score of

patients in whom an initial response was not sustained for six weeks.

### Effect of Histamine Transdermal Cream

Overall, 67 percent of patients responded to the histamine cream, with roughly one-third having a significant response and one-third having some response, as defined above. The results for 55 patients are summarized in Table 2. In practical terms, “significant response” translated to symptomatic improvements such as the recovery of the ability to move an affected limb, an increase in the strength of an affected limb, disappearance of numbness, recovery of the ability to stand without assistance, increased ability to transfer or reposition oneself

in bed, recovery of the ability to walk, recovery of the ability to drive an automobile, increased walking distance, decreased falls, or recovery of bladder control or significant decrease in urgency and frequency of voiding. Roughly 10 percent of patients commented they had seen an improvement in every symptom of their MS.

Several patients were able to return to work full or part time. Patients recording “some response” still had marked improvements, but fewer symptoms were seen to improve.

Numerous beneficial effects, not addressed by the visual analog scales, included decreased sensitivity to heat, decreased fatigue, improved sleep, mood elevation, increased ability to concentrate, decreased peripheral edema, decreased chronic pain, relief of fibromyalgia-type aching, normalization of bowel function, and, in one case, healing of a refractory decubitus ulcer. In many cases,

**Table 2: Response to Transdermal Histamine Patch**

Significant response	19/55 (34%)
Some response	18/55 (33%)
No response/dropped out/ response < 6 weeks duration (9/5/4)	18/55 (33%)

1 denoted minimal or absent symptomology. A significant improvement in a given symptom was recorded if the six-week score was three or more units less than the initial score for that symptom. An overall “significant response” was recorded for the patient if significant improvements (as defined above) were seen in three or more symptoms, and “some response” was recorded if significant improvements were seen in one or two symptom scores. Patients who elected to stop treatment before the six-week follow-up were recorded as “no improvement,” as were

symptom improvement began within hours or days of starting the treatment, with improvements continuing to accrue into the second and third months of therapy.

### **Adverse Events and Effects of Transdermal Histamine Therapy**

Overall, transdermal histamine therapy was safe and well tolerated, in keeping with the extensive experience accumulated with intravenous histamine fifty years ago. Two patients on histamine therapy were hospitalized for what appeared to be unrelated reasons. Both patients were on concurrent intraspinal Baclofen. One patient had a seizure complicating febrile urosepsis; the other developed marked spasticity after the battery on her implanted Baclofen pump failed. One patient with a previous history of hemorrhoids and recent bright red rectal bleeding experienced diarrhea and additional bright red rectal bleeding after therapy had been started. A subsequent colonoscopy was normal. One patient with multiple chemical sensitivities experienced right-sided facial swelling after eating an apple contaminated with an herbicide spray. It is unclear whether this had any relation to histamine usage. Another patient with a history of hives on heat exposure experienced hives after attending an outdoor concert in 105° F weather. One patient on high-dose oral Baclofen became irritable and had a loss of appetite after starting histamine, with a return to previous status upon cessation of therapy.

Rash at the site of application was common, but rarely troublesome. Other negative symptoms infrequently experienced included transient headache, sleep disturbance, diarrhea, and abdominal discomfort. One patient stopped treatment because of diarrhea. No patient experienced new onset asthma, exacerbation of existing asthma, development of an ulcer, or GI bleeding attributable to the treatment.

### **Discussion: Proposed Mechanisms of Action of Exogenous Histamine**

Clinical improvements with transdermal histamine are seen to appear on two time scales. In some cases, improvement manifests rapidly, within a few hours or days of starting therapy; other improvement appears more gradually, over a period of one week to three months. The effects are reversible, with cessation of therapy resulting in a gradual return to the previous level of functioning; reinstatement of treatment results in improvement. Improvement can be broad spectrum with patients who respond well to the treatment experiencing improvement in virtually every symptom. Any discussion of the mechanism of action of histamine must be able to explain these findings. The authors propose the following five ways in which histamine might act:

- Increased concentration of histamine in the synaptic clefts of histaminergic neural synapses (presuming a synaptic deficit of histamine).
- An improvement in the electrical properties of demyelinated fibers.
- Cerebral vasodilation and increased oxygenation of cerebral tissues.
- Modulation (down-regulation) of the pathological immune response, passively permitting enhanced repair (myelination).
- Active stimulation of myelination.

### **Conclusion**

Preliminary investigation with transdermal histamine at the Tahoma Clinic has indicated the intervention appears to be effective, at least for short-term amelioration of a variety of symptoms of MS. In addition, the therapy appears to be well tolerated by most patients. A detailed discussion of the proposed mechanisms of action of histamine in the treatment of MS will be presented in Part 2 of this article.

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