Bee Venom Therapy and Low Dose Naltrexone for Treatment of Multiple Sclerosis

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Treatments for multiple sclerosis are still being investigated despite the long history of the disease. Some disease-modifying drugs were introduced into clinical practice during the last decade. However, their high cost, low safety profile, and most important, limited benefit drive many patients to discontinue these treatments and seek alternatives. This paper describes two alternative treatments that appear particularly effective — bee venom therapy, and low dose naltrexone.

Key words: bee venom therapy, low dose naltrexone, multiple sclerosis

Multiple sclerosis (MS) is a chronic neurological disease characterized by inflammation, demyelination, and axonal degeneration in the central nervous system (CNS). Typical symptoms are spastic paralysis, blurred vision, paresthesias, and incoordination. Emotional disturbances complicate the clinical picture of MS patients, and intensify problems in their daily pursuits.

In the mid 1990s, recombinant interferons for multiple sclerosis were introduced into clinical practice. However, these drugs did not live up to their expectations. It soon became apparent that their primary effects were a modest reduction of the rate of exacerbation in relapsing-remitting MS during the first two years of administration, without preventing the progression.[45] A synthetic amino acid polymer, glatiramer acetate, had no benefit on MS progression and relapse rate, though it was safer than recombinant interferons.[41] Cytostatic agents like mitoxantrone or methotrexate have been associated with increased risk of leukemias and cardiotoxicity.[22,38] Various human monoclonal antibodies against inflammatory cytokines and adhesion molecules or their components (e.g. Adalimumab and Natalizumab, a human monoclonal tumor necrosis factor-alpha antibody, and an antibody against alpha-4-integrin of the adhesion molecule VLA-4, respectively) may provoke opportunist infections like tuberculosis[49] or multifocal leukoencephalopathy caused by reactivation of the JC virus.[42] The benefits of immunomodulating drugs like statins and immunoglobulins have been questioned.[50.55]

As a rule, these treatments affect only immunological and magnetic resonance imaging (MRI) parameters of MS, and provide little actual relief of symptoms. When patients feel nothing but side effects, they become depressed and discontinue treatment. When MS patients perceive positive benefits from treatment, this provides the most favorable psychological setting for further improvement. We would like to describe here two alternative treatments — bee venom and low dose naltrexone — that appear enormously beneficial in relieving multiple sclerosis symptoms.

Bee Venom Therapy For MS

Apitherapy, the medicinal use of honey bee products, has been practiced since ancient times. It was described by Hippocrates (*circa* 400 B.C.) and Galen (*circa* 130-200 A.D.), who used honey, bee venom, pollen, propolis, and other substances in their medical practice. Today, honey bee products are widely used to treat arthritis and other inflammatory, autoimmune, and degenerative diseases.

Bee venom therapy (BVT) is widely used against MS in the hospitals of Japan, South Korea, Taiwan and other Far East countries, although not recognized by Western medicine.[34] In the West, bee venom therapy for multiple sclerosis has largely been folk-medicine. In recent years,

Effects pf BVT	Possible Mechanisms Mediating These Effects
Immunomodulation	Stimulation of phagocytosis and complimentary activity,inhibition of rosette formation and migration of white blood cells
Inhibition of myelin damage	Antiinflammatory effects of melittin, MCDP and phospholipase A2. Antianoxic effects of bee venom components Is mediated by their combination with pollen and royal jelly
Remyelination	Bee venom contains 18 of 20 essential amino acids necessary for the synthesis of myelin
Restoration of physical activity	Improvement of neurotransmission through nerve fibers
Treatment of MS-related blood coagulation syndrome	Anticoagulant and fibrinolytic effects of bee venom
Improvement of mental condition	Analgesic effect of adolapin, stimulation of endogenous opioid production, sedative effects of tertiapin and secapin

Table 1. Possible beneficial effects of BVT for MS according to Prof. I.V. Krivopalov-Moskvin and co-workers.

however, positive changes have taken place. Since 1992, bee venom therapy has been used to treat multiple sclerosis in Chelyabinsk city, Russia. Over 2000 MS patients have been treated in a special treatment and rehabilitation center under the guidance of Prof. I.V. Krivopalov-Moskvin. The primary positive effects of BVT for MS, according to Prof. Krivopalov-Moskvin, are presented in **Table 1** (http://www.api-centre.ru). Prof. Krivopalov-Moskvin concluded that only 5-7% of MS patients showed no improvement after application of BVT.

Some antioxidant and immunomodulating properties of bee venom have been known since the 1980s. Hadjipetrou-Kourounakis and Yiangou reported that constituents of bee venom inhibit the activation of T and B cells, and possibly the activation of an endogenous virus which might induce an adjuvant-related disease[23]; Somerfield and colleagues showed an antioxidant action of bee venom, which inhibited production of superoxide anions by neutrophils.[53] Quite recently, Castro and coworkers published a phase I study of the safety of BVT for MS patients.[10] Nine patients 21 to 55 years old with progressive MS received intradermal injections of bee venom over one year. Three patients experienced subjective improvement, two others experienced objective improvement. In four patients, however, symptoms worsened: the reasons of the observed negative reactions remain an enigma. However, no reliable conclusions could be made about the efficacy of the treatment because of the small number of patients (six women and three men) investigated. Moreover, the authors did not specify the sites of the bee venom injections or other essential information (use of other honey bee products, vitamins, and avoiding some nutrients).

The recent article by Wesselius, et al., described no benefit from bee venom therapy for treatment of MS.[56] Physicians used MRI to monitor brain lesions and measured some symptoms including fatigue. MS patients received up to twenty stings each session, three times a week, applied to the thighs (the exact stinging points were not indicated). Dr. M. Simics, a member of the American Apitherapy Society (AAS), recently commented on the study by Wesselius et al. M. Simics noted that 24 weeks is not enough time to observe any improvements detectable by MRI.[52] He also remarked that not all the MS patients received the same bee venom from the viewpoint of quality and quantity, because these parameters vary significantly with the season of the year. Simics also noted that Wesselius et al. did not use the proper amount of necessary vitamins (namely, the amount of vitamin C was significantly lower than suggested by Mraz[40], while B vitamins were not used at all). Furthermore, contraindicated foods (alcohol, tobacco, sugar, coffee, red meat and milk) and other useful supplements (pollen, bee-bread, royal jelly, and propolis) were not mentioned. Thus, Simics concluded that the lack of positive results of BVT for MS in Wesselius et al. was due to inappropriate experimental design. The investigators should be thanked, however, for their willingness to examine the effects of BVT.

Bee venom contains a variety of peptides (melittin, apamin, mast-cell degranulation peptide (MCDP), secapin, tertiapin, adolapin, protease inhibitor, procamine A, B, minimine, cardiopep, compound X), enzymes (phospholipase A2, hyaluronidase, acid

phosphomonoesterase, glucosidase, lysophospholipase), active amines (histamine, dopamine, norepinephrine, serotonin) and other components with possible adjuvant action in MS patients.[40] For example, melittin, the principle substance of bee venom, is one of the most potent anti-inflammatory agents known (100 times more potent than hydrocortisol). Adolapin, another strong anti-inflammatory substance, inhibits cyclooxygenase; it thus has analgesic activity as well. Apamin may significantly inhibit the activity of C3 complement, and blocks calcium-dependent potassium channels, thus enhancing nerve transmission. Compound X, hyaluronidase, phospholipase A2, histamine, and MSDP, are also involved in the inflammatory response of venom, with softening of tissue and facilitation of flow of other beneficial substances to damaged areas of nervous tissue.[40] Recently published studies suggest that the anti-inflammatory and analgesic properties of bee venom therapy are related to modulation of adrenoreceptor activity and serotonergic neurotransmission.[31,34,35,57] Local inflammatory reactions due to bee stings may increase the sympathetic tone favorable for neuroimmunomodulation of MS.[20] Moreover, bee venom contains much tryptophan[47], which has positive effects on MS.[26]

Special attention should be given to histamine. Bee venom contains about 1% histamine.[28] Histamine treatment for MS originated with Bayard Horton at the Mayo Clinic in the 1940s. Its greatest success was at the MS Clinic of St. Joseph Hospital in Tacoma, Washington from 1946 to 1959. Over 3000 patients with MS and related conditions were treated with the CNS vasodilator histamine diphosphate. Most of them improved, and the disease often stabilized.[24] Histamine injections were also effective in acute attacks and relapses.[11,12] Although some side effects occurred (e.g. headache), histamine was well tolerated in general. Unfortunately, vasodilation therapy for MS fell out of fashion after the 1950s.

Recently, however, Gillson, et al., tested a transdermal histamine cream, Prokarin, usually applied to the anterior thigh with a skin patch.[17,18] MS patients showed decreased sensitivity to heat and chronic pain, reduction of fatigue, improved sleep, elevation of mood, increased ability to concentrate, and other positive effects. Possible mechanisms of histamine's action were presented in a companion paper.[18] A recent report by Packard and Khan[43] described histamine effects on Th1/Th2 balance. The authors claim that histamine plays a significant role in upregulating anti-inflammatory cytokines including IL-4, IL-5, IL-10 and IL-13.[43] Jutel et al. suggest that the primary allergic components of bee venom — histamine and phospholipase A_2 — induced IL-10 production by Th-2 cells and suppressed T-cell proliferation.[29]

As stated above, other bee products should be used along with bee venom. Pollen and bee-bread may improve liver function and strengthen the heart, as well as provide amino-acids to the nervous system. They should be taken as pollen extract, as bee-bread, or pollen in combination with honey (1 part pollen : 1 part honey, or 1 part pollen : 2 parts honey). The first week after meals, the second week before meals, and the third week and later between meals. Pollen administration causes production of the cytokine IL-10 by $CD4^+CD25^+$ regulatory T cells thus favoring the Th1 to Th2 shift.[15]

Honey gives energy to the whole body, cleanses the digestive system, softly stimulates the immune system, cures skin wounds, and relaxes tight muscles. If there is no diabetes, patients can take up to 60 grams a day, before meals, in water or ideally in herb tea. The best honeys are honeydew honey, poli-floral honey, and linden honey. Al-Waili and Boni reported that honey reduces the activities of cyclooxygenase-1 and cyclooxygenase-2, thus showing anti-inflammatory effects.[2] Honey also demonstrates antioxidant and immunomodulatory activity.[3,4]

Royal jelly has been proven to improve the quality of cellular regeneration, fight autoimmune diseases, and increase longevity. The best royal jelly is fresh, taken directly from a queen's cell, but the pharmaceutical forms are also effective. 100-600 mg a day is recommended, according to your condition, in two or three doses, 30 minutes before meals. Immunomodulatory effects of royal jelly were reported recently.[32]

Propolis, known worldwide as an excellent immune-modulating agent, also stimulates the thymus, and has anti-viral, anti-inflammatory, regenerative, and anti-toxic properties; it strengthens the body's cellular membranes. Propolis can be taken in raw form (5-7 grams a day) or in a 20-30 % tincture (10-20 drops, three times a day) between meals, in a spoon of herb tea. MS patient may eventually add 2-3 grams of raw, un-processed and unfiltered honey. Caffeic acid phenethyl ester, an active component of propolis, has antioxidant properties — it diminishes production of reactive oxygen species (ROS) by suppressing nuclear factor kappa B activation and by directly inhibiting inducible nitric oxide synthase.[27] Other beneficial effects of propolis on human health were recently summarized by Lofty.[37]

Thus, apitherapy for multiple sclerosis should include the whole spectrum of techniques, from bee stinging to bee products (honey, propolis, royal jelly, pollen, etc.) and special diet. In some cases, apitherapy has been combined with medicinal plants: stinging nettle (*Urtica dioica)*, calendula *(*Calendula off.) and milfoil (*Achillea millefolium*) as well as Echinacaea tincture and powder of bladderwrack *(Fucus vesiculosus)*.[5] Considering the lack of systemic allergic reactions, bee venom therapy for MS demonstrates, in general, very good results, primarily improvement of motor activity, bladder control, and decreased fatigue. Undoubtedly, bee venom therapy should be considered a first line treatment when multiple sclerosis is diagnosed.

Low Dose Naltrexone For MS

Naltrexone (17-(cyclopropylmethyl)-4,5-alpha-epoxy-3,14-dihydroxymorphinan-6-one) is an opioid-receptor antagonist used primarily to treat alcohol and opioid dependencies (daily dose 50-150 mg). It was first synthesized in 1963 and patented in 1967 as "Endo 1639A" (US patent no. 3332950) by Endo Laboratories, a small pharmaceutical company in Long Island, (NY, USA) (www.gazorpa.com/history.html). Naltrexone and 6-beta-naltrexol (its active metabolite) are competitive antagonists at mu- and kappa-opioid receptors, and to a lesser extent at

delta-opioid receptors. This reversible blockade or attenuation of opioid receptors is the basis of its effectiveness against opioid dependence.

The history of low dose naltrexone (LDN) for treatment of autoimmune disorders began in 1980 when New York physician Dr. Bernard Bihari used it to maintain patients with AIDS. A daily dose of 1.75 mg LDN prevented further progression of AIDS (these results were presented at the IV International AIDS Conference in Stockholm, June 1988). Experiments then showed that MS sufferers might also experience relief from LDN. The first MS patient of Dr. Bihari has had no progression of her disease since she began taking LDN over 15 years ago. Since that time, there has been increased interest in LDN. The first international conferences on LDN was held in 2005 at the New York Academy of Sciences (USA), and the second in 2006 on the campus of the National Institutes of Health, in Bethesda, Maryland (USA). All materials from these conferences including audio and video files are available at www.lowdosenaltrexone.org.

At present, over 3,000 MS patients have been prescribed LDN by their family doctors or neurologists. Most of the Information on dosage and effects was obtained from the LDN websites and newspaper articles and books such as:

www.lowdosenaltrexone.org;

www.ldninfo.org;

www.ldnresearchtrust.org;

www.crystalangel.org;

www.skipspharmacy.com/ldnprez/ldn.html;

www.msrc.co.uk;

www.gazorpa.com;

The Herald (www.theherald.co.uk), April 12, 2004, "MS victim finds hope in heroin users' drug; Campaign launched for urgent trials of naltrexone";

The Sunday Business Post (www.sbpost.ie), May 10, 2004,-"MS Experimental Drug Could Save State Millions of Euro";

The Brattleboro Reformer of Brattleboro, VT (www.reformer.com), May 15, 2004, "Drug Offers Hope for MS Patients";

The Columbia Spectator (www.columbiaspectator.com), May 1, 2004, "Coping with an unprofitable cure";

The Eastern Daily Press of Norfolk (www.edp24.co.uk), May 21, 2004, "MS Sufferers Campaign for Drug Aid";

The Sunday Herald (www.sundayherald.com/52279), October 16, 2005, "This drug could help MS victims... but they can't get it";

The Auburn Journal (daily newspaper of Auburn, CA), May, 2006, "Lake of the Pines woman finds pain relief from MS with experimental drug"; and

Mary Anne Boyle Bradley "Up the Greek with a paddle. Beat MS and many autoimmune disorders with low dose naltrexone (LDN)", Publish America, NY, 2005.

The recommended initial dose of LDN is 3 mg daily between 9 p.m. and midnight, and after a month a dose of 4.5 mg daily for life. Introductory side effects may include disturbed sleep with vivid, bizarre and disturbing dreams, fatigue, muscle spasm, and pain. However, these should disappear after a week of LDN administration. If the 3 mg initial dose causes too prominent or persistent side effects, the dose can be decreased to 2 or 1 mg until the body adjusts. In general, LDN users experience fewer spasms and fatigue, improved bladder control, improved heat tolerance, and improvements in mobility, sleep, pain, tremor and other symptoms. During LDN treatment, no immunodepressants (e.g the interferons Rebif, Avonex and Betaseron) or glucocorticoids should be administered.

It is widely believed that the main benefits of LDN in multiple sclerosis are due to increased levels of beta-endorphins that help maintain immune balance. Beta-endorphins are endogenous opioid peptides with important regulating functions in the CNS.[9] Receptors for these neurotransmitters have been detected on immune system cells.[39] Beta-endorphins are also able to decrease cAMP in immunocytes when it is high, and increase cAMP when it is low. Thus, these neurotransmitters may modulate levels of cAMP.[30] At present, it is known that beta-endorphins may be synthesized both in the CNS and in immune cells.[8,44]

MS patients show lower values of beta-endorphins than normal individuals, deficiency of the neurotransmitter correlates with type of disease.[20,21] Similar findings were observed in patients with rheumatic arthritis and Crohn's disease. Some authors suggested that beta-endorphins may stimulate anti-inflammatory cytokines.[25,48] Interestingly, direct injection of beta-endorphins into the brain of mice infected with neurotropic murine coronavirus (a virus causing encephalitis and paralytic-demyelinating disease in susceptible strains of mice and rats, thus a model for human demyelinating diseases such as multiple sclerosis) resulted in significant reduction of virus replication in the brain.[19] It should be noted here that LDN also shows positive effects in cancers.[7,36,58,59] Therefore, it is possible that LDN acts as a neuroimmunomodulator rather than an immunoactivator or immunosuppressant.

It is now widely accepted that MS is caused by overactivity of immune system. However, Dr. Bihari asserted that the immune system of MS patients should be stimulated, not inhibited. Recent experimental data indicates that the immune system of MS patients shows premature senescence.[54] If this true, stimulation of the immune system might be useful. Dr. Bihari suggested that LDN provokes an increase of T-helper and T-supressor cells, which restores the normal balance of T cells. Other recent evidence indicates that boosting the immune system improves the condition of patients with another Th1 autoimmune disease — Crohn 's disease.[33] By the way, Mraz also suggested that bee venom may boost the level of beta-endorphins.[40]

However, not all agree that MS is an autoimmune system. Chaudhuri and Behan contend that MS is a metabolic and neurodegenerative disease, and that oxidative stress is the final pathway for neurodegeneration.[13,14] Other authors also suggested to administer neuroprotective agents like Co-enzyme Q_{10} (Shults et al, 2002) and carnitine participating in mitochondrial metabolism (Beal, 2003).[6,51] Agrawal (2005) proposed that the benefit of LDN might be anti-

Parameter	Bee Venom Therapy	Therapy With Low Dose Naltrexone
Dose	Dose depends on age, sex, stageof disease, type of physical abnormalities, reaction on bee stinging, coexistent diseases.	Constant dose regardless of stage of disease and physical abnormalities
Duration of treatment	Usually a few courses a year; duration of each course is about a few months (continuous use of bee venom is contraindicated). However, courses should be taken for many years.	Continuous treatment (throughout life)
Diet	Special diet is required	Special diet is unnecesary (however, increased consumption of antioxidants and some minerals is desirable)
Side effects and precautions	Before beginning treatment, however, patients should be tested for allergic reaction to bee venom. Patients with heart disease should take BVT with care.	Initial side effects are most common (disturbed sleep with vivid, bizarre and disturbing dreams, fatigue, muscle spasm, and pain). People with liver or kidney problems should take LDN with care
RESULTS AFTER THERAPY	Increase in sense of well-being, improvements in mobility, bladder control, and sleep, pain, tremor; reduction of fatigue, pain, tremor and spasticity, prevention of disease progression. Remyelination and significant diminution of relapse rate are possible	

Table 2. Comparison between bee venom therapy and low dose naltrexone for MS.

inflammatory, by inhibiting the activity of inducible nitric oxide synthase.[1] Decreased formation of peroxynitrites means less inhibition of glutamate transporters, thus preventing the death of oligodendrocytes from glutamate excitotoxicity.

Conclusions

Patients with MS need long-term management. Reduction of the relapse frequency without preventing the progression may compromise the treatment. MS patients are very sensitive. They should feel that a method really works, and symptomatic improvements should be evident. Otherwise depression may develop after an unsuccessful treatment. Low dose naltrexone and bee venom allow MS patients to perceive real changes. Of course, BVT and therapy with LDN changes one from another **(Table 2).** However, despite the differences between these treatments, many MS patients attest to their effectiveness at preventing further progression. Thus, the discussed treatments combine rapid effects and possibility to manage the MS pattern for a long time.

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