



## **The Need for Trials of Low Dose Naltrexone as a Possible Therapy for Multiple Sclerosis** **Interview with Dr. Yash Agrawal, M.D., Ph.D.,** **University of Iowa**

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Throughout the history of patient experience with multiple sclerosis, a variety of treatment options have been explored. Some of them have proven more effective than others in decreasing the frequency and severity of periodic relapses, although none has been shown to halt long-term progression of disability. Unfortunately, many of the established treatments are very expensive, require the patient to receive frequent injections, and have significant side effects. Generally, the existing treatments are only effective in treating the relapsing remitting form of MS, and do not address the more serious progressive forms of MS.

Within the last few years, there has been growing interest in low dose naltrexone (LDN) as a possible treatment for MS. Naltrexone is an inexpensive oral medication that was approved by the FDA in 1984 for the treatment of alcohol and opiate addiction, using a typical dose of 50 mg/day. The use of LDN in treating MS was first proposed in the mid 1980s by Dr. Bernard Bihari, a board certified neurologist based in New York City. In his clinical practice, the Harvard educated Bihari found that a low dose of naltrexone (1.5 to 4.5 mg/day) taken at bedtime seemed to benefit people with MS and several other conditions with few side effects.

Dr. Yash Agrawal is an Assistant Professor at the University of Iowa. He has recently written a paper titled "Low Dose Naltrexone Therapy in Multiple Sclerosis" which will be published in an upcoming issue of the journal "Medical Hypotheses." Dr. Agrawal's paper is the first medical journal article to directly address the possibility of treating MS with LDN. Boston Cure Project volunteer Robert Lester recently talked with Dr. Agrawal to get some more details on his hypothesis of how LDN may be beneficial in treating MS, to learn more about the current state of LDN usage in the MS community, and to discuss the rationale for initiating formal clinical trials.

**Note:** *LDN has not been formally studied as a therapy for MS and is therefore not an approved therapy for the disease. The Boston Cure Project does not endorse or recommend any specific treatment for any disease, and people considering any therapy should consult with their doctor to obtain professional advice.*

*Dr. Agrawal, the idea of treating MS with LDN is spreading rapidly among the patient community because of a grass roots effort on the Internet and a large community of enthusiastic lay people. This is obviously very different from the way in which traditional medical research and drug discovery is done. Should this "bottom up" phenomenon concern us, or is it to be welcomed?*

For the "bottom up" approach to succeed, it requires an open-minded physician. Throughout the history of medicine, the best clinicians have made their mark by avidly listening to and observing patients. With the advent of the Internet and easy access to information, patients have become very well informed. The practice of

medicine is changing rapidly. Smart physicians should not feel threatened, but instead go back to their roots and listen to what the patients are saying.

*Unfortunately, there is an established history of ineffective or even harmful treatments being tried for MS. This has led to a deep skepticism of any new therapy by both the medical establishment and the patient population. Why is that, and what signs are there that LDN could actually be a realistic treatment for MS?*

This is a very important point. There are many issues. First, the diagnosis of MS is challenging and misdiagnoses do happen. Thus, in some cases a patient could take virtually any treatment and observe a lack of progression/relapses of their MS. Secondly, the snake-oil salesmen prey on MS patients. Physicians rightly brush aside any thoughts that the patient may have of trying such remedies. Thirdly, the common forms of MS are characterized by waxing and waning of symptoms. So patients may feel that a particular remedy is working, while in reality it is just the natural process of their MS.

You ask – what makes me suspect that LDN is the real thing? At this point, neither I nor anyone else can give a definitive answer. This answer can only be learned after a proper clinical trial. But I ask you, can there be smoke without fire? As a very skeptical person myself, I offer the following for consideration.

Firstly, the main proponents of LDN are not involved in selling the remedy; therefore there is no profit motive for them. Rather, they are the thousands of individual MS patients who have found benefit, and they spread the word due to their own unshakable conviction about LDN. Some of these stories can be read at [www.LDNers.org](http://www.LDNers.org) in the US or at the LDN trust site [www.ldnresearchtrust.org](http://www.ldnresearchtrust.org) in the U.K. Highly motivated patients who have failed conventional therapies and were going downhill maintain these web sites. Go through these web sites and consider the effort they have expended in doing all the surveys, establishing a trust, the fund raising efforts, etc. Why would they do it? What might be their motivation?

Secondly, the LDN movement is picking up steam. Consider that one pharmacy alone (Skip's Pharmacy in Boca Raton, Florida) reported dispensing 2508 patient-months of LDN during the period January 1 to August 16, 2004. If one assumes 30 capsules are taken per month, this implies a total of  $30 \times 2508 = 75,240$  capsules. In a prior quote from the same pharmacy dated October 23, 2003, Dr. Skip Lenz reported: "As I have said before, if I had MS, the only drug that I would absolutely be taking is LDN..... In 4 years of dispensing LDN, with over 10,000 patient months, I have heard of only three cases of exacerbation... this is truly a no-brainer. I would find someone to prescribe it no matter the cost or effort." While skeptics would equate this with the extreme gullibility of MS patients, an alternate explanation might be that perhaps it works.

As a third example, [www.remedyfind.com](http://www.remedyfind.com) collects patient initiated reports, which show an overwhelmingly positive response to LDN. These findings appear to have been independently confirmed in a survey by Samantha Wilkinson of LDNers.org. She surveyed hundreds of patients from 16 countries worldwide. She reports a relapse rate of approximately 0.2/year in relapsing remitting MS, as well as benefit in other types of MS. Now I must emphasize, the results should be interpreted with a

grain of salt as this study was done by a patient and can in no way be equated with a proper clinical trial (see LDNers.org for survey results).

Finally, it appears that the existing ABCR drugs are no miracle either. The Cochrane Database, after analyzing all published trials, reported: "Glatiramer acetate did not show any beneficial effect on the main outcome measures in MS, i.e. disease progression, and it does not substantially affect the risk of clinical relapses. Therefore its routine use in clinical practice is not currently supported." Regarding the use of interferons in RRMS, they were more charitable: "The efficacy of interferon on exacerbations and disease progression in patients with relapsing remitting MS was modest after one and two years of treatment." (Both quotes are from the Cochrane Database of Systematic Reviews, 4: 2004.)

*How widespread do you believe LDN usage is among MS patients? Why do you suppose a fairly large number of MS patients are willing to try LDN, especially given that there have been no formal clinical trials of it?*

Precise numbers for LDN usage are hard to come by. I have reported in my article (Medical Hypotheses, in press, 2004) that **one** pharmacy in the US alone shipped 70,000+ capsules over an 8-month period. LDN is becoming increasingly popular in the U.K and worldwide. A Google search reveals over 30,000 hits for the word "low dose naltrexone," some in a variety of languages besides English. LDN is being used in at least 16 countries (based on the survey by Samantha Wilkinson of LDNers.org). A survey of over 1300 MS patients at [www.thisisms.com](http://www.thisisms.com) shows LDN is more commonly used than Betaseron and is running neck and neck in usage with Rebif amongst the survey participants. An important caveat to note when interpreting such surveys is that there might be a "selection bias" in favor of respondents who prefer LDN to other drugs.

LDN is popular because it is inexpensive, oral, has minor side effects, and offers the possibility of stopping progression of MS (at least in some patients). Trying LDN is a no-lose situation for most patients.

*As described in your upcoming article, your hypothesis about how naltrexone may be beneficial in MS is based on its ability to prevent oxidative damage, which some researchers now believe to be responsible for neurodegeneration in MS. Could you summarize this hypothesis and explain what oxidative stress is?*

The area of free radical biology and oxidative stress is quite complex. A good introduction to oxidative stress and MS is the recent article by Gilgun-Sherki (J Neurol 251:261-68, 2004). At the risk of oversimplification, free radicals are certain chemical species that steal electrons from other molecules. This loss of electrons from the molecule is referred to as oxidation, and the causative free radicals are called oxidizing agents. Free radicals are created in the environment, or may be man-made. For example they may be produced by exposure to cosmic radiation, cigarette smoke, or from cellular metabolic processes. The classic free radicals are the hydroxyl, the superoxide and the nitric oxide radicals. Some other relevant species such as hydrogen peroxide and peroxynitrites are not free radicals but can help produce free radicals. Together, this group of chemical species is referred to as reactive oxygen species (ROS). Neuronal cells are normally able to defend themselves against ROS. However, when the neuronal defense system is

overwhelmed by ROS, it results in oxidative stress. Oxidative stress causes damage to protein, lipid and DNA in the cell by this process of oxidation.

The neurotransmitter glutamate is another factor involved in the “excitotoxicity,” or toxicity by excitation of neuronal cells. Glutamate stimulates various receptors in the brain, commonly abbreviated as NMDA, AMPA, and KA. This excitatory effect of glutamate can cause neuronal degeneration by oxidative stress and other mechanisms. Usually glutamate is released in the neural cleft, but part of it may also originate from activation of microglial cells.

*How does all this fit in with damage to oligodendrocytes and the production of scar tissue in MS?*

Oligodendrocytes are the myelin producing cells. Glutamate causes excitotoxic death of oligodendrocytes via the AMPA/KA receptors. This is well established in the experimental mouse models of MS, but less well established in the human model (Wosik K. et al, Brain 2004). Wosik’s claim that human oligodendrocytes are not susceptible to excitotoxicity must be taken with a grain of salt. The authors of this paper point out the many caveats in their study (see the last paragraph of the paper, page 2647).

Loss of myelin producing cells will ultimately result in demyelination. The interesting thing is that the demyelinating lesions caused by glutamate are very similar to that observed in MS (see J.Neurol 251; 261-68, 2004 for details). The idea that glutamate and ROS may be important in MS is also suggested by numerous studies that show that peroxynitrites and glutamic acid levels are elevated in the cerebrospinal fluid (CSF) of MS patients. Moreover, direct examination of MS plaques has revealed increased free radical activity and decreased levels of anti-oxidants.

My hypothesis says that stress (including oxidative stress) activates astrocytes/microglial cells. This results in activation of a kinase called the p38 MAPK. p38 MAPK is known to increase the inducible nitric oxide synthase (iNOS), an enzyme required for the production of nitric oxide and ultimately peroxynitrites. Peroxynitrites are known to inhibit glutamate transport in synaptic clefts and adjacent oligodendrocytes by inhibiting the glutamate transporters. Since the transport of glutamate into cells is inhibited, it results in an accumulation of glutamate that causes excitotoxic death of oligodendrocytes. In this eco-system, naltrexone prevents the increase in iNOS, therefore fewer peroxynitrites are produced, and there is less excitotoxic death of oligodendrocytes. The scientific evidence for each of these steps is discussed and can be seen in a diagram, in my article at LDNers.org.

*Your hypothesis differs from what the majority of the medical community seems to believe, which is that MS is an autoimmune condition in which the body’s immune system mistakenly attacks the myelin sheath. Indeed, the interferon drugs used in MS treatments are thought to suppress the immune system in an attempt to slow the disease process. More recent drugs, including the recently approved Tysabri (natalizumab), are based upon newer research that has suggested that MS is related to disruptions in the blood brain barrier. What do you think about this approach to treating MS?*

The idea that MS may not be an autoimmune disease has been propagated by Peter Behan and colleagues (Chaudhuri A and Behan PO. Arch Neurology 61: 1610-12, 2004) in a series of eloquent papers. Dr. Behan's thinking is not mainstream. But, one must ponder, what if he is right? Is this the reason that the standard drugs work so poorly in MS? After all, if the premise for the mechanism of MS is incorrect, one would not expect drugs designed on an incorrect premise to work correctly.

Natalizumab is the latest drug in the MS armamentarium. It is based on the idea that inflammation of brain tissue is an important part of MS pathology. At a simplistic level, natalizumab blocks certain integrin receptors on some types of leukocytes. By blocking these receptors with natalizumab, the inflammatory cells do not reach the brain tissue and/or cannot cause inflammatory damage. With respect to natalizumab, of concern to me are the findings of Barnett and Prineas. They examined brain tissue of MS patients obtained via autopsies and they did not find the typical inflammatory cells (Annals of Neurology, 55:458-68, 2004). Their results imply that MS may not be an inflammatory disease. So if natalizumab works, it may be by mechanisms different from those based on reducing inflammation.

*Naltrexone is classified as an opiate antagonist. What does that mean? Much of the Internet based discussion of LDN's usage in MS is centered on the idea that it boosts endorphin production; in fact that is why LDN is supposed to be taken at bedtime. Furthermore, several teams of researchers have found inverse correlations between endorphin concentrations and MS disease severity. One study even found that administration of beta interferon raised endorphin levels. What part do endorphin levels play in your hypothesis, or do you view higher levels of endorphins simply as a (beneficial) side effect of LDN?*

Essentially, naltrexone blocks the opiate receptors in the brain. As a result the normally circulating peptides (small proteins) that bind to these receptors can no longer do so. This has two types of effects, firstly that these circulating peptides can no longer stimulate the opioid receptors and mediate their action through it, and secondly their levels probably rise, because they are not being used up by the opioid receptors.

An example of a circulating small peptide is beta-endorphin. It binds to the mu-type of opioid receptor. There are some interesting observations in the literature. For instance, beta-endorphin levels are low in blood cells of MS patients as compared to controls and during relapses (J Neurol Neurosurg Psychiatry 74(4): 495-, 2003). So naltrexone could potentially elevate beta-endorphin levels in MS patients. The problem with the beta-endorphin theory as the sole explanation for the mechanism of action of LDN is, "so what," i.e., it is hard to explain why elevation of beta-endorphins should put a stop to MS. It is possible that beta-endorphins play a role, but the science supporting their role is unclear to me. Also such a hypothesis would imply that other activities that increase beta-endorphins such as eating chocolates, cayenne pepper, exercise, etc. should put a stop to MS.

Endorphin secretion follows a diurnal rhythm, with secretion occurring in the early morning. Taking the drug at night ensures that the naltrexone-induced increase in endorphins coincides with the body's own endorphin secretion. Because the endorphins cannot bind to the opiate receptors which are occupied by naltrexone, the levels of circulating endorphins increase, and they likely mediate their actions by

binding to other receptors. Therefore, the elevated beta-endorphins may create a feeling of well being which is observed in many patients, but naltrexone must act on MS by other additional mechanisms.

*Naltrexone is used in much higher doses to block opiate receptors when treating substance abuse. Wouldn't we want to use a similar dose in treating MS since this would more fully block the brain's opiate receptors?*

As the saying goes: "If it ain't broke, don't fix it." As I have said before, blockage of opioid receptors is only part of the story. LDN has other actions, probably relating to the oxidative damage theory. An important point to note is that usage of higher doses will very likely block multiple receptors other than the mu receptors, leading to undesirable effects. This is well known for opioid antagonists such as naltrexone, where even ultra low dose femtogram (for comparison femto= $10^{-15}$ gm, milligram= $10^{-3}$  gm) amounts of naltrexone can potentiate the effects of morphine, and different results are seen at higher doses of naltrexone (see *Neuroscience. 2004;129(3):733-42*). In fact, Pain Therapeutics, a small biotechnology company, is developing such a drug based on the use of ultra low doses of opioid antagonist, PT-901. So the argument that is widely reported on the Internet, i.e. that high doses of naltrexone (5 mg/kg) did not work in the EAE model of MS, therefore, low dose naltrexone cannot work in human MS, is flawed.

The other thing to keep in mind is that the so-called EAE mouse model of MS does not faithfully replicate human MS. So negative results obtained in the mouse model need not correspond to the human situation. Conversely, positive results in the mouse model (e.g. with AMPA antagonists) also do not ensure similar results in humans. The solution is to do a clinical trial, especially since we are fortunate to have an FDA approved drug to begin with.

*If naltrexone can alter the mechanisms behind apoptosis in MS, does this potentially explain why so much anecdotal evidence suggests that LDN may be helpful in a wider variety of conditions in addition to MS?*

I have not explored in any depth the multiple other diseases where LDN has been reported to be useful. However, apoptosis is a central process in many of the diseases in question, especially cancers. Naloxone, a drug similar to naltrexone, has been tried clinically in stroke and Alzheimer's disease where neuroprotection is needed.

*I've read that LDN is already being studied for treatment of autoimmune conditions such as Crohn's disease, IBS, etc.*

You are right; LDN has been used for other "autoimmune" diseases. While we like to call these diseases autoimmune, they may not be autoimmune. For example, we have discussed Dr. Behan's work that suggests MS is not an autoimmune disease. Recent work suggests that even Crohn's may not be autoimmune, in fact certain mycobacteria are believed to be the causative agents (*Lancet. 364(9439): 1039-44, 2004*). I think there is much that we don't know about these diseases, and about LDN. More research is needed.

*Dr. Bihari and other doctors who have experimented with LDN in MS feel that it should not be taken with the interferon drugs, but apparently taking it with Copaxone (glatiramer acetate, co-polymer-1) is OK. Can you theorize why this might be the case? Any thoughts on whether or not LDN would be compatible with natalizumab?*

As for taking LDN with interferons, I have not investigated it. This is Dr. Bihari's observation. He says that interferons are immunosuppressants, while LDN is a stimulant. So the two drugs work in opposite directions.

In the case of LDN with glatiramer acetate, the effects are synergistic, or at least not antagonistic. The beta-endorphin peptide and other peptides that bind to opiate receptors are made up in part of a common sequence of amino acids: *Tyr-Gly-Gly-Phe-Met* or *Leu*. An interesting speculation is that glatiramer acetate, which is a random polymer, may contain occasional sequences of its constituent amino acids (*Glu, Ala, Lys, Tyr*) that are similar to those of the circulating endogenous opiate peptides, and will allow loose binding to the opiate receptors. So, it is conceivable that a small amount of certain random permutations of this polymer bind to the "opiate receptors" in a manner similar to naltrexone. This theory is pure speculation on my part, but it can be easily tested. Administration of glatiramer acetate should result in an increase of beta-endorphins, same as naltrexone.

Regarding compatibility of LDN and natalizumab, I don't foresee any theoretical objections, but natalizumab is still a new drug and much remains to be learned.

*Can you summarize the case for initiating clinical trials of LDN as a treatment for MS?*

Sure. Some of these have been discussed before:

1. Patients frustrated with conventional drug therapy are increasingly turning in droves to LDN. Frequently, this decision is made against the wishes of their neurologist. It is the responsibility of neurologists to prove or disprove the utility of LDN in a clinical trial. They must do it for their own patients. A proper trial may show that LDN does not work; this will prevent patients from using an ineffective therapy. Alternatively, a trial may show that LDN is effective, in which case irreparable harm may result from not taking it in the first place.
2. The fact that such a large number of patients are taking LDN suggests to me that there can be no smoke without fire. This is also reflected in the numerous reports in the public media (see [www.LDNers.org](http://www.LDNers.org) and [www.remedyfind.com](http://www.remedyfind.com)). Many snake-oil remedies for MS have been touted in the past, but none has gained such wide spread acceptance.
3. Two physicians, one in the US (Dr. Bihari) and one in the U.K. (Dr. Lawrence) have independently observed that LDN works in their patient population. In fact, Dr. Lawrence has MS himself and takes LDN for it. Since the drug is already FDA approved and the clinical experience of Drs. Bihari and Lawrence supports it, a clinical trial is the next logical step.
4. If the respected Cochrane Database Reviews ([www.cochrane.org](http://www.cochrane.org)) are to be taken at face value, patients are currently being prescribed ineffective or only modestly effective therapies for MS. When the alternatives are ineffective, what is the downside of doing a trial of LDN?

5. A scientific hypothesis, and a method for testing it, have now been proposed for LDN (see Medical Hypotheses, 2004, in press).

*What would you want to see studied in these trials?*

Any trial should consider the following components:

1. The scientific validity of the hypothesis should be confirmed. That is, the levels of ROS and glutamate should decrease in the CSF upon treatment with LDN. Beta-endorphins may increase in response to LDN.
2. Three main claims are made in favor of LDN: it prevents relapses, it prevents progression, and it provides symptomatic relief. Interestingly, the standard drugs apparently reduce relapses, but do not prevent long-term progression. These claims for LDN should be studied by monitoring the number of relapses, EDSS disability and MRI's.
3. To deal with the ethical dilemma of providing an untested therapy (LDN), and withholding an established drug therapy (ABCRs), one could potentially start off by designing a trial where glatiramer acetate + placebo is compared against glatiramer acetate + LDN.
4. LDN should be tested in RRMS as well as either SPMS or PPMS patients. The RRMS patients will be a sensitive indicator of the ability to reduce the number of relapses, whilst the SPMS/PPMS patients will be better for monitoring progression.
5. Relief of bladder symptoms and general well being due to raised endorphins should be documented.

*There have been many calls from the patient community for clinical trials. What is the current status of these efforts?*

Some of these are listed at [www.LDNers.org](http://www.LDNers.org) and [www.lowdosenaltrexone.org](http://www.lowdosenaltrexone.org). I would, however, prefer that those doing the trials inform the public about them.

*Given that naltrexone is already an FDA approved drug, these trials would presumably be able to leverage existing safety data, especially since we're talking about using a far lower dose. Does that mean that animal trials to study LDN with the EAE model of MS are not necessary?*

The next step should be a human trial. The EAE mouse model, flawed as it is, may be useful at a later stage to determine the detailed biological effects of LDN.

*Can you describe any further research that you are doing (or plan to do) with respect to furthering scientific knowledge on naltrexone and its use in MS or other conditions?*

I have contacted multiple doctors in the UK, Italy, Germany, Australia and the US regarding a clinical trial. Some of this has borne fruit in the form of pending trials. I am planning to further contact various experts, both in this country and abroad, about investigating the merits of LDN. The hope is that some enlightened physicians will be motivated enough to check out LDN.

*Dr. Agrawal, thank you for spending this time educating Boston Cure Project's readers about the possible use of LDN to treat MS.*

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