

Low-dose Naltrexone in the Treatment of Multiple Sclerosis

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Naltrexone is a drug which is referred to as an opiate antagonist. Its normal use is to treat addiction to opiate drugs such as heroin or morphine. A dose for this purpose is usually 150 mg or more per day.

Low-dose Naltrexone (LDN) has been used in the treatment of MS in the USA since 1985, but is relatively new in the United Kingdom. Despite the fact that the drug is at a very low dose, the absence of significant introductory or prolonged side effects cannot be excluded.

This method was devised, and has since been developed, by Dr Bernard Bihari, a practicing neurophysician in New York, USA. Dr Bihari is qualified in Internal Medicine, Psychiatry and Neurology. His address is 29w 15th Street, New York, New York; telephone number: (212) 929 4196; fax: (212) 229-9371.

The main website is www.lowdosenaltrexone.org

The introductory dose is just 3 mg for the first month of treatment. It has been reported that those receiving this drug in the treatment of MS have experienced a range of benefits, such as: reduced spasm and fatigue, and improvements in bladder control, heat tolerance, mobility, sleep, pain, tremor and other symptoms. After this period, in the absence of any introductory side effects, and for greater therapeutic response, the dose may be increased to the current maximum recommended dose of 4.5 mg per day, to be taken between 9 pm at night and 3 am in the morning.

For those unable to tolerate even the 3 mg dose, an ultra-low, 1.5 mg dose is available. This is intended to introduce the therapy more slowly, allowing more time for the necessary endorphin response to develop.

How Naltrexone Works: The benefits of this drug are apparently due to the temporary inhibition of endorphins (a natural pain-killer, produced in the brain). This results in a reactive increase in the production of endorphins, which would expectedly result in a reduction of painful symptoms, and an increase in a sense of wellbeing.

In addition, increased levels of endorphins would also be expected to stimulate the immune system, promoting an overall increase in the numbers of T lymphocytes. This effect has been observed in Dr Bihari's research. This increase in T-cell numbers apparently restores a more normal balance of the T-cells, such that the effects of the disease process are significantly reduced. Thus, it has been observed that, in those suffering the relapsing-remitting form of MS, the number of relapses is reduced, and the rate of progression of the disease is diminished. In chronic, progressive MS (either primary or secondary) there appears to be a similar reduction in the progression of disease symptoms

In fact, Dr Bihari's research suggests that no one receiving this treatment as a regular therapy has experienced a relapse while actually on the treatment. Occasionally, however, there may be a short-term increase in symptoms during, for example, periods of infection or stress, arising from previously active lesions already present in the brain or spinal cord.

Despite these promising findings it must be emphasized that a positive beneficial response to this treatment cannot be assured or guaranteed.

The Use of Low-dose Naltrexone in MS, and the Occurrence of Side Effects

Introductory Symptoms

When starting LDN, there may be some transient, though temporary, increase in MS symptoms, such as weakness, changes in sensation, muscle spasm, pain, fatigue or tiredness. These introductory symptoms may also include some changes due directly to the altered level of brain endorphins, such as disturbed sleep, occasionally with vivid, bizarre and disturbing dreams. These symptoms usually fade and disappear within the first week of treatment, when they are replaced by improvements in specific symptoms.

The early introductory, but temporary, increase in symptoms may also perhaps be explained when we consider the manner in which this drug is expected to work. Contrary to the common belief that MS is due to over-activity of the immune system, MS actually occurs due to a reduction in immune system activity. Specifically, it is the reduction in the number of the suppressor T-cells within the immune system that permits the damaging CD4 helper T-cells to do their harm. Thus, during an acute relapse, the overall number of T-cells is reduced, the normal balance of helper T-cells and suppressor T-cells is disrupted, and the CD-4 helper T-cells tend to predominate. This is the situation most pronounced during an acute relapse, but a similar situation occurs, perhaps to a lesser extent, in chronic progressive MS.

Under the influence of LDN it has been demonstrated that the numbers of T-cells may increase by more than 300%. Thus, when the number of T-cells is initially increased, the overall predominance of CD4 helper T-cells at this time will expectedly increase the intensity of the MS, therefore temporarily increasing some symptoms. However, as the number of T-cells continues to increase, the normal balance of suppressor to helper T-cells is restored, the activity and intensity of the disease process is reduced, and symptoms once again diminish and improve.

In less than five percent of cases treated, increased introductory symptoms may be more severe or more prolonged than usual, lasting perhaps for several weeks. Rarely, symptoms may persist for two or even three months before the appropriate beneficial response is gained. In this situation, the ultra-low 1.5 or 2 mg dose may be introduced to provide a gentler introduction to the method.

Symptoms Related to the Endorphin Response

If the endorphin response is rapid and significant, there may also be some additional symptoms related to an increased level of endorphins, including nausea and constipation. The nausea usually fades within a few days, and may be minimized by temporarily taking a lower dose of the drug until the symptom diminishes. The constipation may take two or three weeks to resolve naturally, during which time some additional supportive measures may be required.

If constipation has been a symptom prior to treatment with LDN, this may be related to the

MS itself, or it may be due to the continued consumption of foods known to promote food sensitivities, such as cow's milk or wheat. Such food sensitivities are known to promote a range of symptoms collectively referred to as irritable bowel syndrome (IBS). IBS symptoms may include abdominal bloating, flatulence, gastric or abdominal pain, diarrhoea or constipation, or a condition alternating between diarrhoea and constipation. IBS may also increase urinary symptoms of frequency or urgency.

If constipation has been a problem in the past therefore, it is vital that measures should be taken to minimize this symptom before starting the LDN. You should eat plenty of fresh or dried fruit and fresh vegetables. Additionally, food sensitivities should be resolved by avoiding the foods most likely to cause the problem, that is, cow's milk and wheat.

Stool softeners, such as Lactulose, Codalax, Docusate sodium (Dioctyl or Docusol) may be used. The bowel stimulants, such as Dulcolax or Senokot may be more effective, but should be used only occasionally, or avoided if possible, as there will be a tendency to become dependent upon these agents.

Bulking agents, such as Celevac, Fybogel, or Normacol may be useful, but tend to be less effective than the stool softeners for this purpose.

Commercial laxatives, which may be bought freely at the chemist's without a prescription, often contain the drug, phenolphthalein. There are many different preparations and brands available. These products should be avoided completely, as the substance is highly addictive, with a rapidly acquired dependency. Although they appear to solve the problem initially, continued use of such products will inevitably make the constipation much worse!

Symptoms Related to the Inclusion of Lactose Filler

It has also become apparent that some patients, using LDN with lactose filler, have experienced increasing muscle stiffness and/or joint pain, after a few weeks of therapy. This delayed increase in symptoms is believed to be due to an increased sensitivity to the lactose filler used in the LDN supplied by some pharmacies.

Martindales Pharmaceuticals Ltd, and many of the pharmacies in the USA routinely provide LDN, using lactose as a filler. Therefore, if you require LDN with an alternative filler, you should specify the nature of the filler required, such as calcium carbonate, on the prescription submitted. Calcium carbonate is a beneficial mineral, which is free of any such sensitivity reactions.

Symptoms Related to the Prior Use of Opiate Analgesics

Occasionally, other transient symptoms have included more severe pain and spasm, headache, diarrhoea or vomiting. These additional symptoms would appear to be associated with the previous frequent use of strong analgesics, which effectively create an addiction and dependency, thus increasing the body's sensitivity to pain.

It is therefore vital that all strong analgesics including the opiates such as codeine, co-dydromol, co-codamol, dihydrocodeine, tramadol, morphine, pethidine or diamorphine etc, should be avoided for at least two weeks prior to treatment with LDN.

Symptoms Related to the Intrinsic Toxicity of the Drug

From records of toxicity studies carried out on Naltrexone in the early 1980's, reversible liver changes have been found to occur only in those receiving doses greater than 300 mg per day. This is, on average, one hundred times the dose used in LDN. That is, the dose of LDN is just 1% of the dose shown to cause even reversible liver changes. However, the possibility of adverse side effects due to the toxicity of the drug cannot be entirely excluded. The likelihood of damaging side-effects is believed to be minimal however, as the drug is used at such a low dose.

The long-term use of LDN has not yet been statistically evaluated by a trial. Such a trial is planned however, and it is hoped that it might be conducted sometime in 2006, when adequate funding has been established.

Thus, in the meantime, due to the remote but possible toxic effects of long-term use of this drug upon the liver and kidneys, it is required that anyone suffering previous liver or kidney problems should report this condition before starting therapy. The risk is believed to be minimal, however, as the dose of the drug is extremely low, when the drug is expected to be metabolized and excreted from the body within three or four hours of ingestion.

Suggested Method of Therapy:

Take the 3 mg starting dose for the first month. If there are no significant introductory side effects at this dose, start the 4.5 mg dose.

If you are unable to tolerate the usual 3 mg starting dose, it may be necessary for you to use the ultra-low, 1.5 mg or 2 mg dose instead, until your body becomes adjusted.

When starting the 4.5 mg dose, if you notice, at any stage, a tendency to increasing symptoms, this may indicate that this dose is too high for you. In this circumstance, you should simply revert back to the 3 mg dose once again. You should then find that these adverse symptoms will once more diminish and the improvements become more apparent.

Contraindications and Special Precautions:

In addition, because LDN stimulates the immune system and many of the drugs routinely used by the NHS in the treatment of MS further suppress the immune system, LDN cannot be used in conjunction with steroids, beta interferon, methotrexate, azathioprine or mitozantrone or any other immune suppressant drug. If there is any doubt, please submit a full list of the drugs you are presently taking so that their compatibility may be assessed.

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