

## **Low-Dose Naltrexone (LDN) for Mood Regulation and Immunomodulation in ASD**

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Naltrexone is a medication used as an opiate antagonist for treating opiate drug and alcohol addiction since the 1970s, FDA-approved since 1985 and now available in generic form as well as in the brand name ReVia in 50mg tablets. At regular dosing to treat addiction, usually 50mg to 150mg a day, it blocks the euphoric response to opiate drugs such as heroin or morphine as well as alcohol.

Opioids are known to operate as cytokines, the principal communication signalers of the immune system, creating immunomodulatory effects through opioid receptors on immune cells.<sup>1</sup> A popular immune classification method is referred to as the Th1/Th2 balance: Th1 cells promote cell-mediated immunity, while Th2 cells induce humoral immunity. Simplistically, the inability to respond adequately with a Th1 response can result in chronic infection and cancer; an overactive Th2 response can contribute to allergies and various syndromes and play a role in autoimmune disease, which most autism spectrum children show on immune testing. The November 13, 2003 issue of the *New England Journal of Medicine* notes: "Preclinical evidence indicates overwhelmingly that opioids alter the development, differentiation, and function of immune cells, and that both innate and adaptive systems are affected." An Italian study done in 1996 by Scifo and Marchetti attempted to correlate immunological determinations and behavioral performance in treatment with naltrexone in 10, 20, and 30mg doses in autistic children, with significant reduction of autistic symptoms noted in 7 out of 12 children. The behavioral improvement was accompanied by alterations in the distribution of the major lymphocyte subsets, with significant increase in normalization of the CD4/CD8 (T1) ratio and an inverse ratio of changes in NK cell activity to plasma opioid levels.<sup>2</sup> A large body of research in the last two decades has pointed repeatedly to our endogenous opioid secretions as playing the central role in the beneficial orchestration of the immune system.<sup>3</sup>

Bernard Bihari, MD, a New York physician studying the immune responses in AIDs patients, discovered that a very low dose of naltrexone, approximately one-tenth the usual dosage, boosts the immune system and helps fight diseases characterized by inadequate immune function, which definitely includes autism. The temporary inhibition of brain endorphins when given a very tiny dose of naltrexone apparently results in a reactive increase in the production of endorphins, tending to normalize the immune system with this elevation, and accomplishes its results with virtually no side effects or toxicity. Naltrexone is considered very safe and has never been reported as being addicting. When LDN is given between 9 p.m. and midnight, the pituitary is alerted and the body attempts to overcome the opioid block with an endorphin elevation, staying elevated throughout the next 18 hours. Studies in human cancer patients show that LDN acts to increase natural killer cells and other healthy immune defenses, and hundreds of multiple sclerosis patients have totally halted progression of their disease for up to 8-10 years or more with regular use of this medication.<sup>4</sup> Restoration of the body's normal production of endorphins in those with cancer or autoimmune diseases is the major therapeutic action of LDN, which needs to be given only once a day between 9pm and 1-2am.

The use of LDN for children with autism spectrum disorders was previously studied in the 1990s, with researchers using from 5 to 50mg daily or every other day. In these trials, researchers were looking for opioid antagonism.<sup>5</sup> Panksepp, Shattock and other researchers noted better results with low doses; studies on higher doses were more equivocal in children, and non-compliance due to the bitterness of the drug posed a problem for children who could not swallow capsules.<sup>6</sup>

For my private clinical studies, Dr. Tyrus Smith at Coastal Compounding created a very effective transdermal cream. This allowed easy adjustment of dosing (some of the smaller kids did better with only 1-1/2mg), the bitter taste was no problem, and the cream could be put on the children's bodies while they slept. The cream is put into syringes, with ½ cc providing 3mg for children or 4.5mg for adults; most adults prefer capsules; both are equally effective.

I completed a preliminary eight-week informal study on 15 of my autism patients May-June 2005 applying 3mg of LDN transdermally between 9 and 12 p.m. Several adults participated also, one with Crohn's Disease and one with Chronic Fatigue Syndrome using 4.5mg nightly. Parents and participating adults reported weekly on the results of the treatment.

Eight of the 15 children in this study had positive responses, with five of these eight having results considered quite phenomenal according to their parents. The primary positive responses are in the area of mood regulation, cognition, language, and socialization. Two small children responded better when changed to 1-1/2mg dosing. No allergic reactions were noted, and the primary negative side effect was insomnia and earlier awakening, usually fairly short-lived. The two adults in the study had very positive responses, with the Crohn's participant reporting that she has been in remission since starting LDN (almost 10 months at this writing).

All of the children in my study were on well-controlled dietary restriction. I have received reports from the e-list I monitor (over 1200 participants now) of about 5-10% of other children (not my patients) having side effects such as irritability, agitation, and restlessness, subsiding as soon as the drug is withdrawn. I queried parents about gluten/casein/soy in the children's diets, as this response is likely indicative of withdrawal symptoms of opioid block though brief. I suspect that children on a strict GF/CF/SF diet are less apt to show this response; this has yet to be tested.

The immediate positive mood/cognitive/relating effects seen in many children starting this intervention is unlikely to be from immune enhancement showing up so quickly. For other autoimmune studies using LDN, the evidence is that the optimum immune response can take four to six months. In private correspondence with earlier autism researchers Drs. Panksepp and Shattock, they postulated that the LDN therapeutic effect with the rebound of endogenous opioids in the brain "loosens up" the opioid social-reward systems so children who were not connecting to the many known opioid based social rewards in the environment begin to respond to those rewards. Both these researchers emphasized the importance of positive social reactions being reinforced and enhanced substantially by social support and encouragement, helping the new behavior become part of positive behavior modification.<sup>7</sup> A significant proportion of children upon starting LDN show not only some increased hyperactivity and sleep changes, but a bout of what seems like "infection activation" in the form of a cold, fever blister, yeast flare-up and other reactions. These do not seem to be contagious and are usually short-lived, followed by a burst of improved language, cognition, and socially seeking behavior. More recent input about this transition effect indicates that it is probably a "perturbation" of the immune status to another level of functioning, and some pathogen levels previously immunosuppressed may be disturbed while immune elements are changing. Now, instead of immediately lowering the dose, I am asking parents to use the full dosage quite soon, which seems to cut down this time of adjustment for most of the children, not all. Some do need to go down in dosage, but I urge parents to try to stay the course if possible as I suspect the maximum immune benefits occur with full dose, whereas the immediate social-reward and cheerfulness effects occur on ultra-tiny doses without maximizing immune benefits for long-term healing.

As an effective, non-toxic, non-addicting, and inexpensive behavioral and immunomodulating intervention, LDN is joining our biomedical arsenal to help more and more children recover from autism as well as helping anyone with autoimmune diseases and cancer. As an FDA approved medication, it must be prescribed and must also be compounded for the tiny dosing required.

Note: A clinical study has just started aimed at not only ASD children but their parents, as it is well known that autoimmunity has a strong genetic component. 70 adults and 30 children are in this 16 week study. Dr. Vojdani at Immunosciences Labs helped devise an extensive immune panel for determining what LDN will do to important immune and autoimmune markers along with weekly self (or parent) tracking of behavior, mood, and physiological functions. Being tested (McCandless Naltrexone Panel) at the beginning of the study and again after 16 weeks on LDN are the following:

- CBC (Complete Blood Count)
- Metabolic Chemistry Panel
- Lymphocyte Subset
- CD4+CD25+T Cells
- IL-10 (Interleukin - 10)
- TGF-Beta 1 (Transforming Growth Factor - 1)
- Natural Killer Cell Cytotoxicity
- MBP - Myelin Basic Protein Antibodies
- MOG - Myelin Oligodendrocyte Glycoprotein Antibodies
- Neurofilament Antibodies

Results of this study will be reported in June 2006. For more information on LDN, see [www.lowdosenaltrexone.org](http://www.lowdosenaltrexone.org) or join [Autism\\_LDN@yahoo.com](mailto:Autism_LDN@yahoo.com).

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<sup>1</sup> Opioids, opioid receptors, and the immune response, Lois Mc Carthy, Michele Wetzel, Judith K. Sliker, Toby K Eisenstein, Thomas J. Rogers, *Durg and Alcohol Dependence* 62 (2001) 111-123

<sup>2</sup> Ann 1<sup>st</sup> Super Sanita. 1996;32(3):351-9, Scifo R, Cioni M, Nicolosi A, Batticane N, Tirolo C, Testa N, Quattropani MC, Morale MC, Gallo F, Marchetti: "Opioid-immune interactions in autism: behavioural and immunological assessment during a double-blind treatment with naltrexone.

<sup>3</sup>"Detection and Function of Opioid Receptors on Cells from the Immune System", Jean M. Bidlack, *Clin and Diag Lab Immun*, Sept. 2000, p 719-723

<sup>4</sup> "Low dose naltrexone therapy in multiple sclerosis," Y.P. Agrawal, *Medical Hypotheses* (2005) 64, 721-724

<sup>5</sup> "Naltrexone and Other Potential New Pharmacological Treatments of Autism," Jaak Panksepp, Patrick Lensing, Marion Leboyer, Manuel P. Bouvard, *Brain Dysfunct* 1991: 4:281-300

<sup>6</sup> "Low-dose naltrexone effects on plasma chemistries and clinical symptoms in autism: a double-blind, placebo-controlled study, *Psychiatry Research* 58 (1995) 191-201

<sup>7</sup> Private correspondence, Paul Shattock and Jaak Panksepp