

NCI Conference: Low Dose Opioid Blockers, Endorphins and Metenkephalins
“Promising Compounds for Unmet Medical Needs”
Executive Plaza North
Bethesda, MD
4/20/2007

Attendees

Jeff Abrams, M.D.
David Gluck, M.D.
Jill Smith, M.D.
Ian Zagon, M.D.
John Hong, M.D.
Nicholas Plotnikoff, M.D.
Burton Berkson, M.D.
Maira Gironi, M.D.
Filippo Martinelli Boneschi, M.D.

I. Introductory Overview – David Gluck, M.D.

The goal of this meeting is to stimulate interest in LDN and encourage government participation. LDN has been presented to big pharmaceutical companies, but there has been little support provided, as LDN is commercially available and it is unclear whether or not there could be patent coverage for a new indication at this low dosage (3mg to 4.5mg).

Naltrexone was approved by the FDA in 1984 in a 50mg dose as a narcotic antagonist, for the purpose of helping heroin or opium addicts. By blocking opioid receptors, naltrexone blocks not only exogenous narcotics but also natural opioids produced by the brain and adrenal glands, beta-endorphin and metenkephalin. Many body tissues have receptors for endorphins and enkephalins, including virtually every cell of the body's immune system. Because the low dosage of LDN causes a blockade for only a few hours, the body responds with a substantially increased output of endorphin and metenkephalin which then becomes available for the entire remainder of the day – these are believed to have an upregulating effect on the immune system, and there has been no accompanying toxicity.

The discoverer of the therapeutic human effects of low dose naltrexone is Bernard Bihari, MD of New York City. In 1986, he ran a small, brief, placebo-controlled trial of LDN in a number of men who had an emerging illness, newly named ARC [HIV/AIDS]. The results with LDN were so gratifying that he left academia and entered private practice, devoted to treating this disease, for which there was no recognized therapy.

In the subsequent years, he has found that low dose naltrexone not only has impressive effects on patients with HIV, but it also appeared to halt the progress of every autoimmune disease for which it was used, and it was having equally impressive results in the majority of patients with virtually any form of cancer. The extensive summaries of accumulated patient data that Bihari shared with me are presented on my website, www.ldninfo.org.

Because LDN appears to halt progression in many patients with multiple sclerosis, its use has been more recently extended to other neurodegenerative diseases, such as Parkinson's disease and amyotrophic

lateral sclerosis (ALS or Lou Gehrig's disease) whose etiology remains unknown but for which there is suggestive evidence of a possible autoimmune mechanism.

Concerning those doctors who were unable to be here today, I want to mention two especially: Dr. Bruce Cree is a neurologist with a special interest in multiple sclerosis. In addition to providing patient care, Cree focuses on the development of novel therapies through clinical trials. Early this year, he and his colleagues at the University of California, San Francisco began the first double-blind, randomized, placebo-controlled, crossover-design study of LDN treatment for multiple sclerosis in the United States. This 17 week study involves some 80 patients and will examine the effects of low dose naltrexone on quality of life measures in MS [as measured by the Multiple Sclerosis Quality of Life Inventory (MSQLI54)].

Dr. Jaquelyn McCandless is a diplomate of the American Board of Psychiatry and Neurology; she is an autism specialist, and an author. She has already made three notable contributions to today's area of interest: First, she has pioneered the use of low dose naltrexone for children with Autism Spectrum Disorders [ASD]. And along with that, she helped make LDN available as a transdermal cream that is particularly useful for these children. Over the past two years, the treatment has been used successfully for some 5000 autistic children, principally under her direction.

Second, because of her interest in the immune aspects of autism, Dr. McCandless ran a study in 2006 to determine the effects of low-dose naltrexone on an array of laboratory immune values over a period of 16 weeks' use. The participants were 20 ASD children and 38 adults (primarily parents or older siblings of ASD children). The CD4+ T cell count results were of special interest: In the children's group, 18 of the 20 moved higher, only one moved lower, and one stayed essentially the same. It was concluded from the binary test that LDN had a significant positive effect on CD4+ T cell counts at a 99% confidence level. Among the 38 adults, CD4+ T CELLS increased an average of 13% (a 99.5% level of significance). Twenty-six of the thirty-eight participants increased their CD4 levels, while staying within normal limits, twelve went down and one stayed about the same. There were no abnormal values at the beginning or end of the study. So, here is a suggestive study from McCandless that says the use of LDN (which is a nontoxic, oral or transdermal medication, with virtually no significant side effects) appears capable of strengthening the key immune elements one would want to be able to strengthen in people with HIV infections.

Her third contribution is potentially the most important. A clinical trial of LDN for the treatment of HIV-infected people in a developing country is finally about to happen. It will take place in northwestern Africa, in the country of Mali, in its capital city, Bamako, possibly beginning as early as next month (May 2007). Dr. Jaquelyn McCandless, along with her husband, have committed to funding the trial, and the Mali Government has been explicit in its support as well.

And regarding LDN in HIV infections, a notable effect of LDN that emerged in Bihari's practice after ARV's became generally available was that none of his patients on HAART plus LDN developed lipodystrophy – not any! The only exceptions that proved the rule were 2 or 3 pts who, for one reason or another, discontinued LDN either because they had moved away and it was not available to them or because on HAART they deemed it no longer needed. They called Bihari to complain of the lipodystrophy signs and, when restarted on LDN, very gradually experienced a reversal in their lipodystrophy.

To conclude, here is the situation at present: a small family of related therapies is emerging that promises to mobilize the enormous power of the immune system against HIV, cancers, autoimmune disorders, neurodegenerative diseases, and even the common cold. These medications are safe, nontoxic,

inexpensive, available and effective. Unfortunately, the time-honored system for bringing new medicines to the public has failed to work in this case. Big pharma has persevered in demonstrating no interest whatsoever. Perhaps these medications would challenge too great a number of big pharma's existing drugs.

Whatever the reasons, we hope that alternate pathways can be found that will finally permit clinical testing of low dose naltrexone and related medications in a broad array of diseases, so that FDA approval of all of the many uses can eventually be achieved.

Recommended sites: www.remedyfind.com - Records ratings of drugs and LDN has the highest ratings for MS.
www.casehealth.com - Has reports from patients who were treated with LDN (experiences, etc.).
www.ldninfo.org - Detailed information about LDN.

II. Clinical experience with LDN in Crohn's Disease/ Pancreatic Cancer – Jill Smith, M.D.

Dr. Jill Smith presented both clinical and animal trials with LDN. Crohn's disease is a chronic remitting inflammation of the intestinal tract, with a peak during the 1st and 4th decades of life. Crohn's is prevalent in 100-200 per 100,000 people in North America and Europe. There about approximately \$2 billion dollars spent in medical costs currently in the USA, with a significant morbidity rate and decreased quality of life. The symptoms of Crohn's disease include, but are not limited to abdominal pain, diarrhea, weight loss, anemia, malnutrition and fistulas/fissures.

Etiological hypotheses include persistent infection, defective mucosal integrity, dysbiosis and dysregulated immune response. Genetic influences range from familial occurrences, polygenic susceptibility, NOD-2 mutations on chromosome 16 and cytokine cluster region on chromosome 5 and phenotypic correlations. Environmental triggers play a large role in the onset and reactivation of the disease, such as antibiotics, acute infections, NSAIDS, smoking, diet, and stress.

Medicines for IBD: Aminosalicylate, steroids, antibiotics, immunomodulators and anti-TNF α : infliximab and humira. There are problems with the current therapies, in regards to suppression of the immune system, cost, compliance and intravenous infusion of infliximab. Opioid receptors have been identified on inflammatory cells and macrophages; but the role of opioids and their antagonists in various inflammatory states has not been thoroughly studied. Opioid antagonists at low doses have been shown to increase endogenous enkephalin and endorphin levels in tissues and result in healing, i.e., corneal ulcers.

Animal studies with Naltrexone: The effects of naltrexone were evaluated in DSS induced colitis in mice. The mice received DSS in their drinking water and were treated with naltrexone s.c. for 6 days (6.3 μ g/kg or 350 μ g/kg). Their colons were excised and examined histologically. The RNA was extracted and evaluated for cytokine expression. Results: colonic inflammation was reduced by naltrexone.

Human studies with Naltrexone: Phase 2 prospective open-label feasibility study. The purpose was to test the safety and toxicity of naltrexone in subjects with active Crohn's disease. The inclusion criteria included some of the following; active Crohn's disease with a CDAI \geq 220, proven Crohn's disease histologically, endoscopically and radiographically. Infliximab was not allowed and participants had to discontinue infliximab at least 8-weeks prior to initiation of the study.

Treatment: The patients who met inclusion criteria were treated with naltrexone 4.5 mg qhs for 12 weeks followed by a 4-week follow-up off medication. The subjects stayed on baseline medications during study at the same doses and infliximab was not allowed. In order to evaluate a response, blood tests for inflammatory markers, CDAI scores, and quality life surveys were evaluated monthly. A response to treatment occurred when the CDAI scores decreased by 70 points, and remission was categorized with a score of 150 or less.

Results: 17 subjects completed the pilot study. 2 subjects with open fistulas had closure. 2 subjects discontinued routine medication and one flared. The other did well and continued on naltrexone alone. Overall, after LDN therapy, there was a statistically significant improvement in CDAI scores, improved Quality of Life, increased chance of remission, decreased blood inflammatory markers and minimal side effects.

Advantages of Naltrexone: (1) May be administered orally, (2) Down-regulates but does not eliminate proinflammatory cytokines, (3) few side effects, (4) once a day dosing, (5) Cost effective.

New Crohn's Disease Study: Clinical Phase 2 placebo controlled trial, Sponsored by NIH and Broad Medical Research Foundation - PI: Jill Smith, M.D.

Study Design: Part 1: Subjects are randomized to either naltrexone or placebo for 3 consecutive months.
Part 2: After 3 months, all study subjects will be treated with naltrexone and followed for response for 3 additional months.
Part 3: After termination of drugs, the subject will be followed for 1 month off medication to determine the durability.

Randomization criteria: CRP greater than 2.5 or less than 2.5 (normal <0.8)
Site of disease: small bowel only, large bowel only and both large and small bowel

Sample size: 40 subjects, 20 patients per arm

III. Opioid Growth Factor (OGF) in Pancreatic Cancer – Jill Smith, M.D.

Only 9% of people are diagnosed in the early stages since there is no adequate screening for pancreatic cancer. It is resistant to standard chemotherapy and radiotherapy. Vital blood vessels and nerves are in close proximity and the pancreas has no capsule. Pancreatic cancer is more aggressive than any other adenocarcinoma. With risk factors ranging from cigarette smoking, high fat diet, chronic pancreatitis, and familial (hereditary pancreatitis - 30% incidence), Lynch II Syndrome, and others such as Gardners syndrome and von Hippel Lindau. There are several problems with chemotherapy for pancreatic cancer. It does not improve survival (i.e. Survival with gemcitabine is 5.6 months, survival with 5-FU is 4.5 months). There is bone marrow and GI toxicity and it alters the quality of life.

Opioid Growth Factor (OGF) is an endogenous pentapeptide [Met⁵]-enkephalin. It regulates cellular growth and repair of normal tissues and cancer. It also inhibits growth of human pancreatic cancer through a nuclear-associated receptor call OGF_R.

OGF: Phase I Clinical Trial: Sponsored by NIH Grants
R03-CA80646, K24-CA82304, JPS
M01-RR10732 GCRC
FDA IND #: 50,987
IRB#: 97-175

Goals of the study: Safety and toxicity of OGF
Determine the MTD
Compare route of administration (IV -vs- SC)
Examine the safety of administration
Evaluate Quality of Life

Results: Acute Part – The MTD when OGF was given over 30 minutes was 250 ug/kg with hypotension being the dose limiting toxicity. The MTD was not reached with the subcutaneous injection due to solubility but higher weekly dosed were administered and no bone marrow toxicity was reported.

Results: Chronic Part – 16 patients were treated. The infusion rate slowed from 30-45 minutes. No hypotensive events were reported. No laboratory toxicities were found. There was a trend towards improved quality of life. 2/16 subjects with resolution of liver metastases.

OGF: Phase II Clinical Trial: Funded by FDA Orphan Drug (FD-R-002341)
IRB protocol #96-219

Study design: Open-labeled study
Treatment: OGF 250 µg/kg weekly IV
50 subjects total

Eligible patients: Unresectable pancreatic cancer, failed or refused standard
therapy and Karnofsky status 50%

Results: To date, there are 23 patients enrolled and treated. 4 patients were evaluated and not enrolled. OGF was well tolerated. Quality of life appears better than chemotherapy. The weeks of treatment ranged from 1-27 weeks. Thus far, 2 patients are alive on therapy; one regression of primary tumor, some decreases in CA19-9 noted and there is a stabilization of disease.

Conclusion: Treatment of pancreatic cancer is a challenge. Opioid growth factor inhibits growth of pancreatic cancer in culture, mice and humans. OGF appears to improve survival in human subject and improve Quality of Life. The combination therapy with gemcitabine has potential with promising results. More research is needed in the area of opioids and treatment of various cancers.

Potential Problems of Phase II:

1. End-stage at enrollment
2. Significant tumor burden
3. Difficult recruitment
4. Having a control group for comparison

IV. Anti-inflammatory and neuroprotective effects of naltrexone and its analogs - John Hong, Ph.D.

Dr. Hong covered the development of Novel Therapy for Neurodegenerative Diseases.

Glial cells are key players in disease and prime target for therapy. He discussed neuroprotective and anti-inflammatory effects of morphinans and went into detail about neuroprotection by stimulating the release of neurotrophic factor from astroglia and anti-inflammation through the inhibition of microglia-overactivation.

Development of novel anti-inflammatory therapy for Parkinson's disease.

Rationales: (1) Current therapy (L-DOPA) does not slow the progression of PD. (2) Clinical trials show anti-inflammatory therapy of PD is effective. (3) However, due to low potency and safety issues, current anti-inflammatory drugs are not suitable for long-term therapy. (4) More potent and safer anti-inflammatory drugs are urgently needed.

Conclusions:

1. Microglia – anti-inflammatory effect: Microglial NADPH oxidase is the site of action for morphinan-elicited neuroprotection.
2. Astroglia – Neurotrophic effect: Astroglia are the source of neurotrophic factors.
3. Animal studies: Potent neuroprotective effect in various rodent PD models.
4. Preliminary clinical trials: Potential benefits of DM in various inflammation-related diseases.

Research Aims:

- Creation of progressive and inflammation-mediated rodent Parkinson's disease models
- Elucidation of mechanisms of inflammation-mediated neurodegeneration: role of microglia
- Development of novel therapy for Parkinson's disease

V. Overview of Metenkephalin actions - Nicholas Plotnikoff, M.D.

Since the mid-1980's, low dose naltrexone (LDN) has consistently demonstrated a markedly beneficial effect in the treatment of HIV/AIDS. There are a score of such patients who, even today, continue to successfully use only LDN. LDN has shown itself to be an asset to synergistic therapy that diminishes viral breakthroughs and bolsters the restoration of CD4 cell levels.

Methionine – Enkephalin
Lymphocyte Receptors

Delta: Enkephalin
Up regulation
Stimulation of mitogen response
and blastogenesis

Mu: Morphine
Down regulation
Depression of mitogen response
and blastogenesis

Methionine Enkephalin in the Treatment of Aids-Related Complex, Bihari and Plotnikoff

Substantial evidence shows that endorphinergic systems play a central role in homeostatic regulation of immune function, a 12-week placebo-controlled trial of 2 doses on i.v. methionine enkephalin (MEK) was carried out in 46 patient with AIDS-Related Complex (ARC). No significant toxicity was observed. The high-dose group (125 µ/kg/week) produced significant increase in IL2 receptors. CD56 NK and (LAK)

cells, pokeweed mitogen-induced blastogenesis, lymphocyte percentage, and CD3 cell numbers (all as compared to baseline), a significant increase in CD4 cells and CD8 cells (as compared with placebo), and a significant reduction in total lymph node size. The results suggest that MEK is safe and may have a beneficial immune modulating effect in patients with ARC.

VI. Personal experience with LDN for various cancers – Burton Berkson, M.D., Ph.D.

Dr. Berkson shared his experiences of LDN by demonstrating four interesting cases. The cases showed that LDN is well tolerated and to date, some of the patients suffering from pancreatic cancer, B-Cell Non-Hodgkins Lymphoma are alive and well. All of the mentioned patients received low dose naltrexone at 4.5mg Qhs, in addition to incorporating a healthy lifestyle, diet, supplemented with alpha-lipoic acid and vitamins. The patients reported an improved quality of life and stable disease ranging up to 55 months on naltrexone therapy. PET Scans showed notable improvements for several patients. In some cases where CT showed no major change in tumor size, the PET scan did show a change in uptake after naltrexone was administered which did correlate with clinical improvement. There was not a significant change in the sizes of the tumors, but LDN played a major role in stopping the activity of the disease.

VII. Ongoing pilot study of LDN in MS: Preliminary findings – Maira Gironi, M.D. & Filippo Martinelli Boneschi, M.D.

Dr. Gironi explained the roles of beta-endorphins in MS. Beta-endorphins (BE) are opioid peptides released by the hypothalamus, intermediate pituitary gland and by lymphocytes. Its traditional functions are related to modulation of pain, mood, food assumption and endocrine secretion.

The immunomodulating functions include inhibition of antigen induced T-cell proliferation, down regulation of proinflammatory cytokines, and inhibition of macrophage IL-6 and IL-12 production and secretion.

Beta-endorphin levels were lower in MS patients. The lowest BE levels were in progressive forms, the highest in benign and during relapse. Mechanisms related to BE increase during IFN- β treatment are reset of cytokine pattern (IL-1 and IL-6) and IFN- β induced increase of corticotrophin releasing hormone.

Rationale for the Study: Primary Progressive (PP) MS form is orphan on effective drug; the common involvement of spinal cord explains high prevalence of fatigue, pain, spasticity. This form has the lowest BE levels. A mild, diffuse inflammatory reaction has been shown in PP-MS.

Low Dose Naltrexone is documented to be effective on fatigue, pain and spasticity. The LDN driven BE increase could have an anti-inflammatory effect.

Current Study: A 6-month pilot, open-labeled therapeutic study on 40 patients suffering from PP-MS. Patients will receive 4 weeks of pre-screening, 24 weeks of treatment and 4 weeks of follow-up.

Goals of Study: Evaluate the safety and tolerability of LDN and efficacy on spasticity, pain and fatigue.

Measurements: During the 32 weeks of study, patients are undergoing periodic clinical biochemical, (no MRI), to evaluate any adverse events. Neurological evaluation with scales for spasticity, pain and fatigue are periodically performed. The measurement of PBML BE, before and after treatment will confirm the supposed increase of this opioid during LDN treatment.

Conclusion: Low Dose Naltrexone could be a new drug against MS.