September 26, 2003

William J. Daniel, Esq.
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Re:  Patent Application for Low Dose Naltrexone in the Treatment of Inflammatory degenerative diseases of the neuromuscular system including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease and muscular dystrophy

Dear Bill:

As indicated in prior patents for low dose naltrexone as a drug that, taken at bedtime, produces a number of therapeutic benefits by inducing an increase in serum levels of delta opioids such as beta-endorphin and metenkephalin. Since endorphins play a major role in modifying pathological inflammatory responses and LDN is non toxic we have treated several patients with each of the above diseases to evaluate their response to LDN.

Muscular Dystrophy:

Seven patients (all boys between ages 9 and 18) have started treatment of their MD with LDN. Five of the 7 have Duchenne's MD and the other 2 have limb girdle MD. Duchenne's MD is a genetic disorder that causes progressive muscle weakness as individual muscle cells become inflamed and die. The cause of the muscle wasting lies in a genetic defect in the ability to form an important muscle protein called Dystrophin that leads to the formation of abnormal dystrophin proteins, which by interacting improperly with the other proteins in the muscle cell and muscle cell wall weakens the cell membrane causing a local inflammatory response which causes muscle cell membranes to rupture, leading to contraction of the cells and cell death. Macrophages and cytotoxic CD8 cells arrive to clean up the remnants allowing satellite cells to group together to build new muscle cells. As a boy with Duchenne's gets older the number of dying cells overwhelms the repair capacity of the satellite cells allowing fat and connective tissue to fill in spaces left by the dying cells. Over time the boys developed difficulty in running or walking upstairs. The muscles become loose. Muscle strength gradually declines with losses in the ability to walk, to use hands and arms, the ability to speak and swallow and eventually an inability to breath using their rib muscles and diaphragm. This last development generally leads to death by the age of 20.

In the several other types of MD besides, Duchenne's, a defect in the gene for production of dystrophin occurs but may be less severe. In some cases the genetic defect resides in the genes for sarcoglycan, calpain or myotolin, caveolin and merosin whose functions resembles that of dystrophin.
Patients with MD generally have high levels of creatinine phosphokinase in the blood (abbreviated as CPK or CK) reflecting the muscle destruction.

The widespread use of prednisone to treat MD disease is partially beneficial and is based on its anti-inflammatory effects which underscore the role of muscle change due to the inflammation that follows upon rupture of muscle cell walls by defective dystrophin. Prednisone also an immunosuppressant drug which reduces the role of macrophages and cytotoxic CD8 cells in causing post-inflammatory scarring. Prednisone, however, through it modestly slows disease progression has a number of destructive long term side effects including the development of obesity, diabetes, osteoporosis, arrested growth, weakened defenses against infections and corticosteroid induced muscle atrophy.

Cases:

As of 9/21/2003 seven boys ranging in age from 9 to 18 years have been started on LDN. Four have been on it for less than 2 months (including 2 with Duchenne's and 2 with Limb Girdle muscular dystrophy). These four have shown no sign of disease progression during this time with all experiencing improved energy.

Three boys all with Duchenne's MD have been on LDN for more than 2 months, one for 16 weeks, one for 12 weeks and one for 9 weeks. The first patient C.L. on LDN now for 16 weeks is an 11 year old boy who is mostly wheelchair bound but can stand and take a few steps without help everyday. Before starting LDN he would fall suddenly while standing an average of twice a week. After 7 weeks on LDN his falls began to decrease with only one fall occurring in the last 4 weeks and none in the last 2 weeks. This indicates improved muscle strength in the muscles around the hips. His ability to swim laps has gradually increased from one at a time to 3 at a time and at week 10 he became able to pull himself out of the swimming pool using his arms for the first time in 2 years. General strength in his arms has modestly improved and his ability to lift his head off the bed has increased from a 3 inch rise to a 5 inch rise above the pillow. These improvements at four months on LDN are modest in the context of his overall weakness, but are significant. Before he started LDN his overall motor weakness was slowly but inexorably worsening despite long term therapy with prednisone (which has continued). The second patient D.M. is a ten year old boy with Duchenne's MD who now has as of 9/26/03 been on LDN for 13 weeks. After 7 weeks on LDN, D.M. was able to swim 2 laps at a time instead of just one and at 8 weeks was able to pull himself out of the pool with his arms for the first time in 18 months. The other 5 boys, on LDN for shorter periods of time, have experienced an increase of energy, the beginning signs of increased muscle strength and no progression in muscle weakness.

The clinical benefit of LDN in children with MD seems to become apparent after the first 8 weeks. The mechanism of action appears to be due to reduction in dystrophin induced inflammatory response of the muscle cell wall which otherwise would damage the muscle membrane causing post inflammatory scarring. Presumably the improved function is due to the growth of satellite myofibrils into full muscle fibers. The extent of long term clinical benefit in children with long term MD is as yet unclear. It is clear however that the pathological process leading to loss of muscle integrity, strength and function is arrested by LDN allowing for the possibility of slow replacement of damaged muscle fibers leading to clinical improvement. The crucial element is that the disease activity is arrested by LDN.

Parkinson's Disease:

This is a disease, which occasionally starts with people in their 30's, has a more common onset in the 5th, 6th and 7th decades of life. Clinically, Parkinson's involves gradually increases in rigidity of muscles of the plastic type and relatively constant resistance to passive stretching of the muscles equal in the flexors and extensors. The plastic response distinguishes Parkinson's from spasticity
in which the muscle resistance increases as the muscle is more stretched. If there is muscle
tremor during stretching the classical cogwheel rigidity shows with the muscle reflecting both
rigidity and tremor at the same time. Most Parkinson’s patients have tremor in major muscle
groups while at rest generally reduced or abolished by movement. Parkinson’s is caused by slowly
progressive lesions of the globus pallidus and substantia nigra in which neurons that produce
dopamine are injured in large numbers. The injury begins with an inflammatory process of
unknown cause followed by death of neurons and scarring.
The putamen and corpus striatum are also frequently involved though not as central to the disease
as lesions in the substantia nigra. These neural bodies, all called the basal ganglia, are involved in
modulation-control by the cortex of voluntary movement through a graded inhibition which assists
in the smoothness of cortical control of muscles. Damage to these basal ganglia interferes with
the normal modulation of cortical control of muscles. This leads to rigidity and the development of
tremor. In each case the neuronal bodies involved in the nigrostriatal pathway is dopamine, the
lack of which plays a central role in the manifestation of the disease. Drugs which deplete or block
dopamine such as reserpine, chlorpromazine, haloperidol, and other anti-psychotic drugs may
produce a drug induced Parkinson’s syndrome by inhibiting production of dopamine by basal
ganglia. Partial relief of Parkinsonian rigidity and tremor is provided by oral administration of
carbidopa with levodopa (precursors of dopamine) or by bromocriptine, another dopamine
precursor. These drugs may produce some symptomatic relief but do not stop progression of the
underlying disease. They may also produce side effects, such as involuntary movements,
diskinesia and twitching. The side effects generally limit the tolerable dosage.

I have treated 7 patients with Parkinson’s disease with LDN starting 4 years ago with the most
recent beginning LDN 6 months ago. All 7 cases who are now on LDN an average of 24 months
have shown at least an arrest of the disease progression since starting LDN. Most have been able
to decrease the dosage of dopamine precursor drugs to decrease their side effects without loss of
function. Two of the 7 had unilateral Parkinson’s involving only one side of the body. In both over
a period of several months on LDN there was complete reversal of the clinical deficits. None of the
7 have shown any disease progression, which is otherwise inevitable in Parkinson’s.

It appears that the LDN works by increasing serum beta endorphin and metenkephalin levels
thereby modulating through their immune system regulation the inflammatory process. This
subsequently stops the neuronal scarring that underlies the pathophysiology of the disease.

Since the neuropathology and neurophysiology of progressive supra nuclear palsy, pallido
parametal degeneration and Hollervarden Spatz disease are so similar to that of Parkinson’s
disease they are highly likely to respond to LDN as well as Parkinson’s to LDN.

Alzheimer’s Disease:

Alzheimer Disease results from a progressive cerebral degeneration occurring in middle or late life.
It is the commonest cause of progressive dementia in the middle aged and elderly population.
Some 50-60% of the 3.0 million demented patients in the US suffer from Alzheimer’s Disease with
most of the rest caused my multiple small strokes. The principal pathological changes involve a
profusion of senile plaques throughout the cerebral cortex especially in the frontal lobes associated
with an inflammatory response and intramural fibrillary tangles. Degeneration of nerve cells of the
hippocampal pyramidal layer is quite prominent secondary to the inflammatory response. Cortical
atrophy and enlargement of the ventricles result from the scarring of neurons. There is a
quantitative relationship between the severity of the dementia and the ubiquity and severity of the
plaques and secondary neuron degeneration.

In the early stages the patient suffers a loss of short term memory, becomes careless in dress and
conduct and neglectful of work and family responsibilities. As the disease progresses patients stop
recognizing friends, become disorientated and restless and may wonder about. Speech becomes
sparse and in late stages of the disease speech is slurred. Epileptic seizures may occur and spastic paralysis of the limbs occasionally develops. Duration of the disease from onset to death is generally 18 months to 15 years.

The only treatments available for Alzheimer's Disease represent modest and time limited benefit using cholinergic agents and acetyl choline precursors since the parts of the brain most damaged in the disease use acetyl choline as their primary neurotransmitter. Two small recent studies with nonsteroidal anti-inflammatory drugs suggest that reducing inflammation and the subsequent neural degeneration in the brain may have some benefit in slowing disease progression. Because of the effects of LDN in inducing endorphin production which in turn reduces the inflammatory response we have treated 3 patients with Alzheimer's disease starting 3 years ago. One patient started 2 years ago and one 18 months ago. All 3 were in their 50's or early 60's and had significant impairment in recall and recent memory (short term memory) but had not yet developed seizures, slurred speech or neglect of dress or social behavior. In all 3 cases disease progression was stopped by LDN with each case showing modest improvement in recall and recent memory, reversing the loss of function occurring in the preceding 3 to 6 months. Thus the data so far indicate that LDN can arrest the progression of Alzheimer's disease. Because of the similarities of Pick's Disease in neuropathology and neurophysiology with those with Alzheimer's including the same kind of inflammation followed by scarring in the brain, Pick's Disease should respond as well as Alzheimer's to LDN.

Amyotrophic Lateral Sclerosis (ALS):

This is a disease characterized pathologically by degenerative changes in the anterior horn cells of the spinal cord, the motor nuclei of the brain stem and the cortico-spinal tracks in the spinal cord. Since these are the neurological structures that innervate the muscles these inflammatory changes in neuronal tissue lead to secondary progressive muscle wasting with eventual paralysis and death.

Motor-Neurone Disease is sometimes used as an inclusive term to include variants of the disease that focus on the bulbar spine and the original term "progressive muscular atrophy" characterized by lower motor neuron disease. They represent variants of the same disease with inflammation and degeneration of the anterior horn ganglion cells followed by scarring of these cells with shrinkage of the grey matter of the anterior horns of the spinal cord and wasting of the ventral nerve roots which innervate the muscles. The degeneration is associated with secondary gliosis which represents one of the primary mechanisms of scarring in the nervous system. The cells of the motor nuclei of the lower brain stem show degeneration and gliosis as well. There may be microscopic changes in the cerebral motor cortex with degeneration and gliosis of ganglion cells in the frontal and precentral regions.

Motor Neurone Disease is most often a disease of late middle life, usually beginning between the ages of 50 and 70. The disease is generally sporadic but occasionally has a high family incidence with major genetic factors in causation. In general, the etiology is unknown with no clear viral or environmental causes. An abnormality of microphage migration has been described leading to the inflammatory damage of motor neurons.

The onset of the disease is generally insidious, with the first motor abnormality generally seen in the hands which become weak stiff and clumsy. The muscles begin to waste and fascicular twitching may be seen. When degeneration begins in the bulbar motor nuclei the first symptoms involve problems with speech and swallowing. Muscles of the upper arms and shoulder girdle sometimes weaken first and occasionally muscles innervated by the medulla are first effected with shrinking and weakening of the tongue, the palate and the external muscles of the pharynx and larynx. Pursing of the lips and whistling becomes impossible and saliva runs from the open lips. Speech gradually becomes unintelligible. The muscle paralysis and wasting gradually becomes
generalized with paralysis and wasting of all the body's striated muscles including eventually the diaphragm. Diaphragmatic paralysis leading to respiratory failure is usually the proximate cause of death. There may be modest increases in the serum creatinine (CPK) levels lower than those seen in primary muscle disease such as Muscular Dystrophy. Early in the disease the clinical picture must be distinguished from those of syphilitic amyotrophic, meningitis cystercerosis, spinal cord tumor in the cervical cord area, cervical spondylosis and muscular dystrophy. The disease is progressive with death coming as early as 18 months after onset. Forty percent of patients survive over 5 years but 90% die within 10 years.

There is no treatment yet available specific to or effective in this disease.

Low dose naltrexone offers some possibility of treatment usefulness through its ability to increase serum endorphin levels to reduce inflammation and gliosis and scarring of motor neuron cells. We have so far treated 6 patients with ALS with LDN. All are men in advanced stages of the disease. The longest of the patients has been on LDN for 9 months and the patient on LDN for the shortest time is 2 months. All have shown arrest of disease progression. Five of the six have shown at least a 20% improvement in the forced vital capacity, the breathing test that measures function of the diaphragm. Four have shown modest improvement in ability to move their arms and hands and the ability to hold their head up with neck muscles. It is difficult to predict whether further improvement will occur but it is likely that only the most recently lost functions will improve because of the permanent scarring and loss of nerve tracks and neurons involved in the disease. The LDN however does appear to arrest disease progression in all of the cases so far leading to the hope that with earlier diagnosis ALS associated disability could be markedly reduced.

Sincerely,

Bernard Bihari, M.D.