

## Dr. Ian S. Zagon Introduction to Low Dose Naltrexone (LDN)



Dr Ian S. Zagon and his team

As a scientist, educator, inventor, and university professor at a medical school and health center, it is not often that I get an opportunity to write something for a non-scholarly book or journal - much less to introduce a website listing of testimonials. However, the extraordinary scientific observations already made, along with the realized and unrealized clinical implications of the science insofar as the treatment of a variety of debilitating and often fatal illnesses, provides a compelling stimulus to say a few words about the subject of low dose naltrexone (LDN). And, quite frankly, the history of LDN, the biology revealed about the underlying mechanism of this drug, and the future of LDN deserve mention. Finally, something needs to be said about why it may be difficult to establish LDN as a medically condoned treatment for many diseases - and what it will take to do so.

First, let us discuss the history of what has been popularly called

"LDN". Naltrexone is an opioid antagonist (it blocks exogenous (e.g., morphine, heroin, methadone) and endogenous (e.g., endorphins, enkephalins) from the opioid receptors in your body). When this was first discovered back in the 1960's, the inventors were seeking a non-addictive opioid to relieve pain, and synthesizing a series of compounds that resembled morphine (an important exogenous opioid that is widely used for pain relief). At the time, the investigators (Drs. Blumberg and Dayton) concluded that naltrexone (along with other opioid antagonists such as naloxone) had little value. Only in the 1970's, did the utility of opioid antagonists such as naltrexone and naloxone become apparent in the reversal of opioid overdose, and in the management of patients with addiction to opioids. Today, naltrexone (trade names Revia and Depade) is widely used in the treatment of drug and alcohol dependency. The philosophy of using naltrexone is to employ a high enough dose (e.g., 50 mg) to

block the elevated mood one gets with drugs such as heroin. Naltrexone, at an appropriate dosage, is capable of interfering with opioid-opioid receptor interactions which brings on the "high".

In 1979, my colleague Dr. Patricia J. McLaughlin, Professor of Neural & Behavioral Sciences at The Pennsylvania State University College of Medicine - and a coworker for over 3 decades, glimpsed the remarkable properties of the biological system influenced by opioid antagonists. It took a few years of scientific experiments, however, to arrive at an understanding of what LDN was doing. Basically, LDN - and this is also true for some other opioid antagonists such as naloxone - invokes an intermittent blockade of opioid receptors from native opioids for approximately 4-6 hours/day. During this interval, these native opioids are prevented from interacting with the opioid receptors present on cells in the body; these

cells depend on opioids to govern metabolic processes and to regulate cellular replication (which most cells undergo except for such elements as nerve cells and red blood cells). The body - and cells - react by compensating for this blockade by making more opioids and opioid receptors. Of course, this excess in opioids and opioid receptors still cannot interact with each other while the opioid antagonist is present. However, after 4-6 hours when the opioid antagonist disappears and the blockade is removed because LDN has been metabolized by the liver, the elevated level of opioids and greater number of receptors interact with each other causing a heightened biological reaction. As I mentioned above, this biological reaction involves the governing of processes related to cellular, tissue, and organ integrity, and the duplication of cells. Pertaining to cell growth, this opioid-opioid receptor system in essence acts to keep in check the number of cells through a tonically active inhibitory mechanism (in other words the system is in a constant dynamic state that maintains cell number by carefully monitoring - and restraining if necessary - the number of cells produced). In cancer, for example, an intermittent blockade by opioid antagonists has a profound effect on delaying replication of these deadly cells. In Crohn's disease, patients have been found to become "normalized" while on LDN - we have discovered this in a clinical study recently reported. To round out the story of LDN, in subsequent years we eventually discovered that the endogenous opioid involved with LDN action is called opioid growth factor (OGF) (chemical term - methionine enkephalin - one of the very first native opioids discovered). The OGF receptor (OGFr) mediates the activity of OGF. Treatment with exogenous OGF allows magnitudes more of this potent peptide to react with the OGF receptors, and this substance is currently in Phase 2 clinical trials for therapy of pancreatic cancer, squamous cell carcinoma of the head and neck, and hepatocellular carcinoma.

When we finally understood how intermittent and continuous opioid receptor blockade influenced biological systems, we published two papers in the prestigious journal - *SCIENCE*. Both appeared in 1983. This was really the official heralding of the discovery of the marvelous properties of opioid antagonists, and the announcement that endogenous opioids and opioid receptors, thought up to this time to be only related to neurotransmission in the nervous system, were involved with regulation of homeostasis and growth of cells, tissues, and organs - as well as in abnormal states (e.g., cancer). In addition, Penn State University elected to take patents on this intellectual property. This was our first adventure into the business world. Thus, invention disclosures for these patents were filed around 1982, and full patent applications filed within the year that focused on the extraordinary new uses of opioid antagonists - especially naltrexone. Up to this point, naltrexone was approved by the Food and Drug Administration (FDA) for systemic use in treating patients abusing drugs (especially morphine and heroin) and alcohol, with 50 mg tablets prescribed to induce a continuous state of opioid receptor blockade for 24 hours. For LDN, this had to be estimated using data for the continuous blockade in humans, comparison of published pharmacokinetic reports on the plasma half-life of naltrexone in humans and rodents (our experiments to this point were in mice and rats), and pharmacological, physiological, and behavioral experiments performed on animals that told us how long different dosages of naltrexone - and naloxone - had a functional effect. Our estimations came down to the recommendation of 3-10 mg of naltrexone, daily, to induce an intermittent opioid receptor blockade (and to get the rebound of increases in endogenous opioids and opioid receptors that could interact for 16-18 hours/day). Hence, LDN was born.

Soon after the publication of our initial papers on this subject, I had received telephone calls from several

physicians asking about the clinical implications of our findings. This was extremely flattering. Not knowing about rules and regulations of confidentiality when it comes to patent law (subsequently I learned that a confidentiality disclosure needs to be signed by both parties so that information can be exchanged without violation by another party concerning the patent), I freely - and enthusiastically - told these individuals the entire story (much had yet to be published) and gave out dosages and recommendations for the timetable of a regimen (initially try taking it in the evenings before bedtime to avoid discomfort brought on by deprivation of the body's endogenous opioids with opioid receptors - and if this has repercussions (e.g., disturbing dreams) take it in the morning) for human consumption. I remember distinctly that one physician called me back the next day and related that in the prior evening this individual took the dosage of LDN I recommended and felt terrific in the morning. I was surprised by the will of this doctor to take the drug to see the results, but equally heartened that the drug gave exactly the results predicted - an extraordinary feeling of well-being after the naltrexone had terminated and the elevated levels of native opioids and opioid receptors could interact. This physician experienced what has been commonly called a "runner's high". Little did I know that one or more of these physicians started to use LDN (I do not know how - or when - this term developed, but appears to be how intermittent opioid receptor blockade is known with the use of naltrexone) for patients with diseases that were not treatable. Normally, drugs are prescribed for known uses, and this is governed by the FDA. However, physicians can prescribe a drug for a new use without FDA consent under what is called "off-label" and "compassionate use". Basically, what was going on was that some physicians were prescribing LDN in the hope that endogenous opioid systems (native opioids and opioid

receptors) could be of benefit to individuals with diseases that were otherwise not responsive to known therapies. This "trial and error" practice of medicine began to empirically define conditions where LDN would be of promise. Patients with multiple sclerosis, Crohn's disease, Parkinson's disease, and cancer were just a few that seemed to respond to LDN (remember, this information is anecdotal and no clinical trials have yet to be performed). I would receive telephone calls and letters each week asking about LDN, and with the advent of the internet I began receiving inquiry upon inquiry (sometimes 10-30 a week). I learned that at least one physician was charging \$500 for a 30 minute telephone interview and a prescription for LDN. This type of medical practice (long-distance medicine) really abuses a physician's responsibility and, in some ways, draws the wrong attention to a potentially beneficial drug. I also was concerned that physicians were prescribing LDN in speculation that the drug might help practically any disease.

I discovered that there was an LDN website that attracted a wide audience of individuals with untreatable diseases who were either in a terminal state or chronically ill. These folks were searching the web in the hope to see if others had remedies for their condition. I also began to hear that both patients and physicians were providing misguided information about how the drug worked, and giving rigid instructions as to when and how the drug should be taken (e.g., a dosage of 4.5 mg, only in the evening). Moreover, all of this was in violation of our patents for the use of naltrexone. This brings to the surface major problems with drugs that are off patent (naltrexone was discovered over 50 years earlier) and are generic. Some more background is needed to understand the issues. A patent for a "composition" (specific ingredients of a therapy) provides the legal powers to have highly restricted and regulated use of a drug. This is precisely the value of

having a patent - and a license to a patent. Violators that make and use the drug other than the company licensed, are at risk for unlawful action. Once a patent is over, and there is a new use for a generic drug (as in the case of LDN and the treatment of diseases), there is no easy way of policing the distribution and sale of this drug. Therefore, patents on "methods" may be considered "intellectual property", but in the end, they do not offer an easily enforced protection if others wish to violate such a patent. This is the painful lesson we learned about naltrexone and the regulation of biological processes. Companies were interested in LDN, yet the question of exclusive rights and the enforcement of the patents arose time after time, ending further negotiations. This leaves the public in the precarious position of only having drugs brought to market that will be financially acceptable, and leaves out therapies that - although they may treat a disease - and often at a very low cost - are not in a position to be able to recover expenses and make a profit (i.e., lack exclusivity). The loser in all of this is the public who have diseases that may be treatable by drugs that need clinical trials but this course is stymied by the inability of the drug to be attractive to a commercial venture. In the case of naltrexone, this is one of the major problems. No one ultimately has elected to develop naltrexone for treatment of diseases because it was not a profitable venture, plus the money required to go through the preclinical and clinical phases of a drug far outweighs the potential profits.

The inability of having protection of a generic drug such as naltrexone has significant ramifications for patients in desperate need of treatment. In essence, the way drugs are discovered may be supported by government funding (the most notable is the National Institutes of Health) or other agencies, but it takes significant amounts of money to conduct clinical trials. Let us digress for a moment, and briefly discuss the path of a drug from discovery in a laboratory to use at the bedside. What we call the

route of translational research - discovering a drug and bringing it from "bench to bedside". If one is a fortunate scientist - in a university or industry setting, they may discover a drug that is of potential benefit in treating disease. The preclinical studies often start with a tissue culture model (cells are exposed to a particular agent and examined for an effect), and then progress to the function of the drug in animals (usually mice and/or rats). When animals are studied, there is an Institutional Animal Care and Use Committee (IACUC) that first must examine the proposed experiments and insure that the animals will be utilized in a humane fashion. These animal studies need to follow the guidelines of the FDA, wherein the research scientists have extensive interactions - and understandings - with the FDA as to what is required to take a drug into clinical trials. This usually necessitates toxicity and efficacy studies in two species, often either mice or rats, and rabbits. If successful, the subsequent investigations are performed under what is termed "Good Laboratory Practices"(GLP), whereby a research or pharmaceutical team examines toxicity of the potential drug in at least one species (often rabbits) within strict guidelines; the research laboratory needs to be accredited by an FDA inspection as to whether rules are followed (e.g., laboratory notebooks must be in proper order). If a research laboratory is not GLP certified (and this may cost \$40,000 or more for training), they need to either send their studies to a group that is GLP certified, or call in specialists to train the research team as to GLP standards - with final certification granted by the FDA after testing. The FDA usually requires assessment of toxicity at three different dosages (one dosage that is toxic, another that is not toxic but is efficacious, and another that is neither toxic nor efficacious), with toxicology testing performed on tissues to examine drug presence and concentrations. I might add that along the way, prior to publication, presentation, or announcement of the discovery of the drug - or

method of use of a drug - intellectual property agreements must be sought. In essence, within the U.S. for example, one needs to file an Invention Disclosure with the U.S. Patent office prior to any public disclosure of the drug, and within one year must file a full patent application.

If the drug passes the FDA requirements with preclinical trials under GLP standards, clinical trials are needed to establish the safety and efficacy of a new agent. Before clinical trials on a new drug - or new indication at a different dosage - may begin (e.g., before the drug or biological may be shipped across state lines), the sponsor must file an IND (Investigational New Drug application) with the FDA. In the IND application, the sponsor of the clinical trial must provide the FDA with substantial evidence that the drug has been manufactured with certain requirements, that the drug can be provided to the clinical investigators with consistent purity and potency, and has received approval of the animal testing cited earlier as well as anticipating potential toxicity in humans and drug metabolism and excretion. Additionally, the IND specifies the protocols of the initial clinical trials. The clinical trials generally proceed in three distinct phases, with each phase having specific goals and features. Even before a discussion of these trials can take place, one more oversight group must approve the protocol - the Institutional Review Board. This is a group of individuals from the hospital/medical center that includes physicians, pharmacists, biomedical scientists, administrators, statisticians, nurses, and other concerned individuals that carefully review the proposed protocol for safety. Once this approval has been obtained, the clinical trials can be initiated. In Phase 1, safety and dose are examined on a small number of patients, generally 15-100. The goal is to define a safe dose and delivery schedule, with a maximal tolerated dose (MTD) being determined. Phase 1 studies often take no longer than 6 months to one year to

complete. If Phase I is successful as determined by the FDA (and this can range up to 70% of new drugs), Phase 2 trials that are related to the effectiveness of the drug are undertaken. Phase 2 trials are generally conducted in a randomized, double-blind, controlled fashion. The term controlled means that some patients receive the drug under investigation, while others receive a placebo (an inactive material that generally is the vehicle the drug is composed in) or the currently accepted standard of care treatment for the condition. Randomization means that the assignment of patients for the experimental and control arms will be entirely by chance and that the groups are matched (gender, age, disease state). Double blinding means that neither the patients nor the physicians/nurses/health care providers involved in the study know whether the patient is taking the drug or the control; only designated persons - often the statistician and an investigational pharmacist) know whether the drug or the placebo is being utilized. This procedure insures that assessment of safety, toxicity, and efficacy are made without any conscious or unconscious bias on the part of the patient or health care provider. The purpose of Phase 2 trials is to test in a scientifically rigorous manner with statistical methods whether a drug is more effective than the control. Phase 2 studies often involve 100 or several hundred patients and may take several years to complete; around 33% of these drugs successfully pass Phase 2 testing. Phase 2 trials are the essential step in indicating the usefulness of a drug, and determining the need for a Phase 3 trial. Phase 3 trials are more extensive testing using the same procedures as in Phase 2 - randomized, well-controlled, double-blinded evaluations. Phase 3 studies may involve up to thousands of patients, be conducted in a number of different locations, and take 1 to 4 years to complete; around 25% of the drugs clear this hurdle. So, at the end of roughly 5 years of clinical research, and with 5-8% of drug submissions making it to this stage,

a sponsor assembles all of the relevant information about the drug, including the manufacturing, animal safety testing, and the results of the clinical trials, into a new drug application (NDA) to be submitted to the FDA. This NDA can run 10,000 to 100,000 pages in length. The FDA has reviewers that carefully examine all of the data, and usually take 1 year for review and decision. All of this time the clock is ticking away at the 20 years from the date of filing a patent available for exclusive rights, and perhaps 10-15 years have passed. This leaves a pharmaceutical company a short time to recover the staggering costs (up to 1 billion dollars) to develop a drug from concept to the market.

Where does that leave us with LDN. First, LDN is a generic drug. This already does not make it valuable to a drug company because it is not patent protected. Second, even a "use" patent for LDN is difficult to enforce in terms of restrictions because the drug is generic. In essence, this means that a new use for naltrexone will be difficult to go through the process of FDA approval. This approval is extraordinarily important in protecting the patient, as it provides information about drug interactions, the maximal tolerated dose, side-effects, timing of drug administration, and the diseases - and stages of diseases - a drug is effective in treating. Therefore, we have come to a major impasse with LDN. A drug that costs \$1/day has remarkable properties that brings relief to the suffering of so many. What is needed is some mechanism needs to be invented to bring this drug to the marketplace. Exactly how the financial structure of this need is met is another question. Whether generic drugs can receive a new patent for other uses, and if these patents can be enforced so that drug companies or investors become interested in taking on the expense - and risk - of developing a drug is a matter of governmental concern. At present, the Federal Government will sponsor preclinical trials, Phase 1 clinical trials and, in part, Phase 2 clinical trials. However, it is the next step (Phase 3)

that is most critical in bringing drugs to the marketplace. And one that the Federal Government will not fund.

Finally, on this Website, we have dramatic testimonials that individuals with untreatable diseases - or family/relatives/friends of these individuals - seeking information from others by using the internet. In other words, these patients are gaining medical advice from others suffering from the same disease, and who have found relief by various treatments. Information about LDN, including LDN websites, proliferate. Patients desperate for cures - or relief of their misery - latch on to the stories of others who are testifying that a drug or procedure has done wonders for them. The upside of the web is that there will be drugs/treatments outside of conventional medicine that are indeed safe and efficacious for some diseases. Moreover, these drugs (e.g., LDN) and/or treatments (e.g., hyperbaric oxygen) may be at relatively low cost. As mentioned earlier, doctors can prescribe these medications on the basis of "off-label" and "compassionate use". Situations in which no other treatment is available, and the physician is acting in the best interest of the patient - yet with trepidation as to whether a drug or treatment will be harmful because preclinical and clinical information is unavailable or scarce at best. The downside of this is that a drug or treatment may not be of value in treating a disease, have side effects that are deleterious to the well-being of the patient, and have negative interactions with other medications or symptoms. With LDN for example, naltrexone is a well-known agent that precipitates withdrawal in individuals taking exogenous opioids such as morphine (e.g., for pain relief). The combination of morphine and LDN could render the individual

with a withdrawal reaction. On a more subtle note, LDN raises the endorphin levels of the body and this is accompanied by a feeling of euphoria. Painful stimuli may be ignored in these individuals, yet these painful signs are really telling the patient and physician of underlying problems. On an entirely different note, these testimonials on the web could be informative to scientists about drugs or treatments that are of value as therapeutic modalities for diseases. These scientists may well heed this anecdotal information in searching for viable therapies. So, this Website raises the question of the practice of medicine for untreatable diseases. In essence, patients are their own physicians because there is little in conventional medical practice left to use. And the numbers of these untreatable individuals are staggering. Over 500,000 individuals in the U.S. each year die of cancer. Chronic pain strikes millions of people. Neurodegenerative diseases like Parkinson's have a prevalence of about 350,000, multiple sclerosis another 400,000 patients and Alzheimer's disease strikes almost 2.5 million people. Where can these individuals turn for relief or hope? Hence, the Web has become extraordinarily powerful about raising hopes for treatment by testimonials of other individuals who offer success with such modalities.

This Website allows patients with life-threatening and chronic diseases - and their families - to begin to navigate through medical strategies by listening to other patients on the internet, seeking medical counsel, and taking action as they elect. They are practicing the old adage: Patient heal thyself. As a biomedical scientist engaged in healthcare, I would hope that patients practicing novel therapies will one day have these treatments validated, and that commercial ventures be encouraged

to bring these therapies to the marketplace where they can be safely and confidently utilized by all. To do this, scientists - basic and clinical - require the funds to perform the required studies. However, the funding of biomedical studies has become more difficult. In fact, some agencies are not funding grants at all. One source of monies is the patient population. As an example, just recently a family presented us with a donation of \$50,000 to pursue research on LDN (and OGF) with respect to multiple sclerosis (MS). It so happens that one of the family members has MS, and is greatly benefiting from taking LDN. So, large or small sums of money donated to your favorite researcher or charity will have meaning. Ultimately, your support is what is needed to push efforts forward to understand the biology and clinical value of LDN and OGF so that it becomes a legitimate tool in medical practice.

We would like to thank  
Dr Ian S. Zagon for this  
document.

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