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| The LDN Research Trust is a UK registered Charity, founded in 2004, with the primary purpose of promoting research into the unlicensed use of Naltrexone at a low dose to treat conditions and diseases. Naltrexone at a low dose is referred to as LDN.  **Formal Disclaimer**  The information is designed to guide patients and enable them to make an informed choice about treatment. It does not replace the need for clinical involvement, and the LDN Research Trust will not support patients who obtain LDN without a prescriber’s prescription.  **Naltrexone Background Information**  Naltrexone has been commonly used at daily doses of 50-300mg since it was first licensed in 1984. Naltrexone has been used in lower doses to treat multiple diseases since 1988. Naltrexone is considered a “standard dose” when given in daily amounts of 25mg or more and low dose when the daily dose is less  than or equal to 10mg. When prescribed in a standard dose, Naltrexone acts primarily to block opiate receptors and as such is used mainly in addictions. Multiple Phase I and II trials have shown efficacy.  **Mechanism of Action**  When used in a lower dose has Immunomodulatory, opiate blocking and anti- tumor effects, and multiple phase, I and II trials have shown efficacy. • Improves the immune system response  • Creates an increase in the production of endorphins, which should result in a reduction of painful symptoms and an increased sense of wellbeing  • Increased levels of endorphins can be expected to stimulate the immune system, promoting an increase in the number of T lymphocytes. This effect was observed in Dr Bihari’s research. This increase in T-cell numbers restores a more normal balance of the T-cells such that the effects of the disease process are significantly reduced.  • It may also act directly on these immune cells to stimulate or restore normal function  • Opiate Blockade for a short period (4-6 hours)  • Levo Naltrexone molecule binds to opiate receptors  • Causes rebound increased endorphin release.  • Increases sensitivity of existing opiate/ endorphin receptors.  • More Opiate receptors are formed to capture endorphins.  **Cancer**   * Intermittent Dosing with LDN causes increased cell death and increases cell sensitivity to chemotherapy agents. * Cells treated with LDN upregulate genes that are responsible for cell death. (BAD and |  |

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|  | BIK1)   * Tumor cells pre-treated with intermittent   LDN dosing are far more likely to be killed by  chemotherapy drugs.   * LDN seems to have a direct cytotoxic effect   on cancer cells via a P13 kinase, cyclin P21 and downstream G-Protein coupled receptor routes.  **Which Diseases Are Being Treated With LDN?**  This list is not exhaustive and patients are directed to the LDN Research Trust website for more information www.ldnresearchtrust.org/ conditions  Autoimmune Hepatitis Inflammatory Bowel Disease (Crohn’s/Ulcerative Colitis) Multiple Sclerosis CFS/ME Lyme Disease Chronic Viral Infections Mast Cell Activation Syndrome (MCAS) Hashimoto’s Thyroiditis Grave’s Disease Chronic Regional Pain Syndrome Parkinson’s Disease Diabetes Type I Vitiligo Scleroderma Psoriasis Anxiety and Depression PCOS Melanoma Nerve Pain (Neuropathic conditions) Glioblastoma Esophageal and Oral Cancers Non-Small Cell Cancer Breast Cancer Multiple Myeloma Lymphoma Ovarian Cancer Renal Cell Cancer Colorectal Cancer Duodenal and Stomach Cancer Uterine Cancer Hepatic Cancer PTSD  PMDD  Infertility (based on the research by Dr Phil Boyle, who is the Director of the NaProFertility Clinic in Dublin, Ireland and the President of the International Institute for Restorative Reproductive Medicine)  **How To Obtain LDN**  Not all medical professionals are aware of LDN, and its potential benefits and not all are prepared to prescribe LDN. It does help to have a knowledgeable LDN prescriber working with you. The LDN Research Trust has a list of LDN Prescribers which can be found here: (https:// www.ldnresearchtrust.org/LDN\_Prescribers). The LDN Research Trust works hard to maintain a support network for prescribers through regular conferences and media events.  LDN is not generally covered by insurance plans but is an affordable prescription through your local compounding pharmacy (https://www. ldnresearchtrust.org/ldn-pharmacists).  **How To Use**  Read this guide before you use this medicine. It includes information that might be especially important for you.   * ·  Keep this guide you may need it again * ·  Ask your pharmacist or doctor for more advice if you need it. LDN comes in several forms: tablets, capsules, liquid, sublingual drops, troches, lozenges, and a cream.   Consult your doctor before using this medication if you are currently taking long- acting opiate medicines like codeine, tramadol, morphine, fentanyl or oxycodone. Do not use this medicine if you are pregnant or breastfeeding without informing your doctor.  •  Dosing Options for LDN – For many conditions, your prescriber will usually start treatment at a low dose and increase gradually over a period of weeks until you are stable at your goal dose. Starting dose can vary from 0.5 mg to 1.5 mg and |

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| is often increased up to 4.5 mg. You may have a lower OR higher dose goal with your prescribing clinician. You may be instructed to take multiple smaller doses on a daily basis for certain medical conditions, such as for mental health conditions. Higher, standard doses of 50mg or more may be required for TBI (Traumatic Brain Injury) patients until they are stabilized before transitioning to daily low doses of naltrexone.   * LDN dosing for patients with chronic pain conditions will start at an Ultra-Low Dose, and you will take the medication twice daily, separating it by 4-6 hours from short acting opioid medications. * For cancer patients, the dose should get to 4.5mg, or the goal dose, although your provider may adjust as necessary. In cancer patients, combining a cannabinoid (CBD) or Sativex (THC/CBD), seems to enhance the anti-tumor effect. No chemotherapy agents are currently contraindicated assuming standard tests are done, however, LDN should not be taken during treatment with immune checkpoint inhibtors (e.g. Opdivo or Keytruda -- PD1 inhibitors)   Storing the Medicine - LDN Liquid should be stored in the fridge once opened and can last 30 days or 12 months if unopened. Capsules should be stored at room temperature in their original container for up to 6 months. All forms of LDN will be labeled with a specific expiration date by your compounding pharmacy.  Only obtain LDN via a doctor’s prescription and a reputable pharmacy - LDN is extensively counterfeited all over the world so it is not safe to purchase it from websites willing to sell it to you without a prescription—it is likely to be fake, or even dangerous, and it is illegal.  **Possible Side Effects**  LDN is well tolerated in most patients. However, care should be taken to titrate the dose up slowly to avoid side effects.  Common:  • Sleep disturbances  • Mild headache • Mild agitation • Nausea/GI effects - consider switching to  liquid sublingual LDN to bypass GI tract • Hyperthyroidism in Hashimoto’s patients  Uncommon:   * Flu-like symptoms (CFS/ME) * Rash * Herxheimer reactions (elevated   temperature)   * Dizziness * Increased fatigue or spasticity (Parkinson’s)   These side effects are usually only present in the initial phase and can be stopped by halving the dose for 2-3 days and then continuing with titration again. The half-life of LDN is about 4-6 hours. Report any side effects to your prescriber.  For Up-to-Date Clinical Trials and References visit - https://www.ldnresearchtrust.org/ldn-clinical-trials   * 1. Brown N, Panksepp J. Low-dose naltrexone for   disease prevention and quality of life. Med Hypotheses. 2009;72:333-337. doi:10.1016/j. mehy.2008.06.048.   * 1. Zagon IS, McLaughlin PJ. Naltrexone modulates tumor response in mice with neuroblastoma. Science. 1983;221:671-673. doi:10.1126/ science.6867737.   2. Zagon IS, McLaughlin PJ. Naltrexone modulates body and brain development in rats: a role for endogenous opioid systems in growth. Life Sci. 1984;35:2057-2064. http://www.ncbi.nlm.nih. gov/entrez/query.fcgi?md=Retrieve&db=PubM ed&dopt=Citation&list\_uids=6092812.   3. Bihari B, Ottomanelli GA, Drury F, Ragone VP. T-cell subsets and treatment response in AIDS. AIDS Res. 1986;2(4):263-266.   4. Bihari B, Finvola DM, Ragone VP, Ottomanelli GA, Buimovici-klein E. Low Dose Naltrexone in the Treatment of Acquired Immune Deficiency Syndrome. 1988; (June).   5. ClinicalTrials.gov. https:// clinicaltrials.gov/ct2/results? term=low+dose+naltrexone&Search=Search. Accessed January 1, 2015.   6. Donahue MJ. Low-Dose Naltrexone (LDN). 1995;(4).   7. Sajben N. LDN World Database. 2011. http:// painsandiego.com/2011/01/19/ldnworld- database/. Accessed February 23, 2015. |  |

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