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REPORT

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Now 21 months old, ALSUntangled (www.alsuntangled.org) has 285 twitter followers and 69 clinician scientists from across six countries participating in 37 open discussions in our NING. New alternative and off-label therapies (AOTs) added to our discussions since our last publication include methylcobalamin, the Stem Cell Rejuvenation Center, and the International Center for Cell Therapy and Cancer Immunotherapy. We have published seven investigations of eight different AOTs being used in ALS. We recently linked with Quackwatch (www.quackwatch.com), a group that has been systematically investigating AOTs used in various diseases for many years. We are also excited to announce a new collaboration with the online community – Patients Like Me (www.patientslikeme.com) – in which we will be able to review their patients' experiences with the AOTs we investigate.

At the request of PALS, we here investigate low dose naltrexone (LDN) as a treatment for ALS.

Low dose naltrexone

Naltrexone is a long-acting competitive antagonist of the mu, delta, and kappa opioid receptors. It is FDA approved for the treatment of opiate and alcohol dependence (1). In the last 20 years, the drug has received attention for other possible effects, whether acting through opioid antagonism or other mechanisms. Specifically, low dose naltrexone (LDN, at 4.5 mg per day) has become a popular AOT for a long list of diseases, including autoimmune diseases such as multiple sclerosis and neurodegenerative disorders such as Parkinson's disease and ALS. There are a large number of preclinical studies of LDN exploring possible effects of blocking opioid receptors. There are no compelling placebo-controlled human studies for any specific neurological disease, including ALS.

Nonetheless, there are vocal advocates, mainly citing pre-clinical data and personal anecdotes, promoting LDN treatment for ALS and other indications. At the top of the lowdosenaltrexone.org website is the statement (2):

> 'FDA-approved naltrexone, in a low dose, can boost the immune system – helping those with HIV/AIDS, cancer, autoimmune diseases, and central nervous system disorders.'

LDN for ALS also remains a frequent topic of discussion on ALS patient forums, with both positive and negative anecdotes (3). Often forum members are referred to the advocacy site above, which emphasizes uncritical promotion.

Plausibility of LDN for amyotrophic lateral sclerosis

The current use of naltrexone is for opiate and alcohol dependence (4). However, research over the last 20 years has revealed that the opioid system is involved in more than just pain modulation. For example, there is now extensive evidence that opioid receptors are present on and exert immunomodulatory effects in a number of immune system cells and signaling molecules (5,6). This includes effects on natural killer cells, T-cells, cytokines, and interferons. The net effect of naltrexone in blocking opioid receptors on immune function is still a matter of research, but it is not implausible that naltrexone can have an immunomodulatory effect, perhaps an immunosuppressive effect. Thus it is at least theoretically possible for chronic low dose naltrexone to have a therapeutic effect on autoimmune diseases.

At present, however, there is insufficient evidence to conclude that LDN is effective for any specific autoimmune disease. Studies in Crohn's disease are promising but preliminary (7). There are several pilot studies of LDN in multiple sclerosis. A 2010 study by Cree at al. showed benefit for subjective quality of life measures but no benefit for physical outcomes (8). This may be due to the short duration of treatment, but also suggests that LDN may provide a subjective effect due to increases in endogenous endorphins, even if there is no disease-modifying effect.

The consensus of current evidence and opinion is that ALS is a multifactorial neurodegenerative disorder.

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An autoimmune component has been investigated (9,10). However, treatment trials with immunosuppressive therapies have not demonstrated any clinical effect in ALS (11–13). Therefore, to the extent that LDN may have a clinically relevant immunosuppressive effect, which itself has not been established, this would still provide a questionable mechanism for any benefit in ALS.

There is evidence of a potential neuroprotective effect of opioid antagonists, mostly from studies with naloxone (which has similar opioid antagonist effects as naltrexone but is shorter acting). Studies have shown a protective effect for motor neurons in rat models of traumatic brain injury (14). However, rat models of ischemic stroke have shown mixed results, with some studies showing a protective effect of opioid antagonists (15) while others show a protective effect of opioid agonists that are blocked by naltrexone and other antagonists (16). A neuroprotective effect for naloxone has not been shown in humans. The mixed findings in animal models of ischemic stroke make any inference to human ALS devoid of factual basis; naloxone might even be harmful for PALS.

Clinical evidence

There are no published clinical trials of LDN or other protocols of naltrexone in ALS or other motor neuron disease. There is one published study with naloxone in ALS – a 1983 pilot study including two subjects with no apparent benefit (17).

Within the Patients Like Me community, 31 patients reported taking it for ALS: 15 completed an evaluation of the treatment with several reporting more than one evaluation – their highest score is reported here. Seven patients (47%) said LDN had no effect or that they were unsure; three (20%) reported slight efficacy, and four (27%) reported moderate efficacy. Reported benefits included a decrease in excessive yawning ($n = 1$), balance improvements ($n = 1$), more energy and less phlegm ($n = 1$), improved speech intelligibility ($n = 1$), and better nasal breathing ($n = 1$). These are non-verifiable reports largely of symptomatic relief. In the absence of placebo controls and masking, they cannot be attributed to LDN. They cannot be used to infer even subjective efficacy in others.

Safety

Reactions reported with naltrexone include 'nausea, vomiting, injection site reactions (including induration, pruritus, nodules and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders' (1). In addition, there is currently a black box warning for possible hepatocellular injury and naltrexone should not be used in patients with acute hepatitis or liver failure. These side-effects and toxicity, however, occur with full dose naltrexone (380 mg injection) and may be less frequent and severe with low dose naltrexone.

Within the cohort of 31 Patients Like Me participants, side-effects reported include vivid dreams ($n = 1$), sleepiness ($n = 1$), increased spasms ($n = 1$), diarrhea ($n = 1$), headaches ($n = 1$), nausea ($n = 1$), hot flushes ($n = 1$). Reported costs range from $25 to $49 per month.

Conclusions

Additional pharmacologic studies of LDN are needed to clarify its mechanisms of action. Some of its proposed mechanisms such as immunomodulation and neuroprotection could potentially be useful in ALS. However, there are no convincing data thus far to suggest that this is the case, and some limited data even raise a theoretical potential for a harmful effect. The benefits reported by a small Patients Like Me cohort are not consistent across participants, nor are they objectively verifiable. A small pilot study of a drug with similar mechanisms found no objective benefits in patients with ALS. Although reported costs are not exorbitant, there are reported and potential side-effects including liver toxicity. ALSUntangled does not recommend LDN use by patients with ALS at this time.

The ALSUntangled Group currently consists of the following members: Steven Novella, Richard Bedlack, Orla Hardiman, Paul Wicks, James Heywood, L. P. Rowland, Merit Cudkowicz, Eric Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Alex Sherman, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Marigakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Terry Heiman-Patterson, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Lisa Krivickas, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Tahseen Mozaffar, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula.

Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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