



# MEA Summary Review: Low Dose Naltrexone (LDN) in ME/CFS

By: Charlotte Stephens 13<sup>th</sup> November 2019

A [recent publication](#) by researchers from Griffith University in Australia examined the possible therapeutic mechanisms of a drug called 'Naltrexone' in ME/CFS patients.

In this summary review, we explain what Naltrexone is, how it works, what it's used for and why it might be useful as a treatment for ME/CFS, as well as discussing the findings from this latest study.

## Key Points

- Naltrexone is an opioid receptor blocker, traditionally used in the treatment and rehabilitation of alcoholism and opioid addiction.
- In much lower doses than its traditional use (known as low-dose Naltrexone or LDN), it is used 'off-label' (unofficially) in the treatment of a variety of chronic illnesses, including Multiple Sclerosis (MS), Rheumatoid Arthritis, Crohn's disease, Fibromyalgia, Complex regional pain syndrome (CRPS) and Sjogren's syndrome.
- Several studies demonstrate its effectiveness as an anti-inflammatory, pain modulating drug that is useful in many auto-immune type conditions.
- The latest study indicates that Naltrexone is able to restore functioning in Natural Killer cells (a type of immune cell that many studies have found to be dysfunctional in ME/CFS) taken from ME/CFS patients.
- Larger studies are needed in order to validate these results.
- Dr. Jarred Younger's team are currently carrying out [a clinical trial](#) for the use of LDN in ME/CFS, which is due to complete in summer 2020.

## News Media Reporting

- Medical Xpress – [Researchers discover potential therapeutic approach to treat chronic fatigue syndrome](#) – by Griffith University – 11<sup>th</sup> November 2019.

# What is Naltrexone?

Naltrexone is a medication that binds to and blocks opioid receptors on cells throughout the body. It is primarily used to treat alcohol or opioid dependence, as it blocks the effects of drugs known as opiates (e.g. morphine, codeine, heroin) and reduces the desire to use these substances.

## Low-dose Naltrexone (LDN)

Low-dose Naltrexone (LDN) is where Naltrexone is taken in much lower doses than are prescribed for its traditional use; usually around 2-10% of the amount used for opioid addiction (Toljan et al. 2018).

It has been suggested that LDN can act as an immunomodulator and may be beneficial for a range of inflammatory conditions, including Crohn's disease, Multiple Sclerosis (MS) and Fibromyalgia (Patten et al. 2018).



Source: Cptinc.org

LDN has been used 'off-label' (unofficially) in the treatment of a range of chronic diseases in the USA since 1985 but is relatively new in the UK and Europe (Ringerike et al. 2015). Although LDN is relatively inexpensive, funding for off-licence prescriptions may not be available via the NHS.

## How does LDN work?

LDN works differently to Naltrexone. At low doses, it only blocks opioid receptors for a few hours. While they are blocked, your body responds by producing lots of endorphins, which are our 'feel good' chemicals and natural pain-killers (opioids) (Sprouse-Blum et al. 2010).

A small dose of Naltrexone can boost endorphin production by up to 300% (Bihari 2013). The increased levels of endorphins can last for 12-24 hours after the drug is taken.

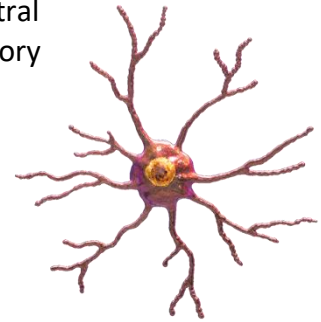
Interestingly, an investigation by Conti *et al.* reported significantly reduced levels of endorphins in ME/CFS patients, reflecting the condition of chronic immune activation.

As well as increasing endorphin levels, several other mechanisms of action of LDN have been reported, including immune-modulating and anti-inflammatory effects.

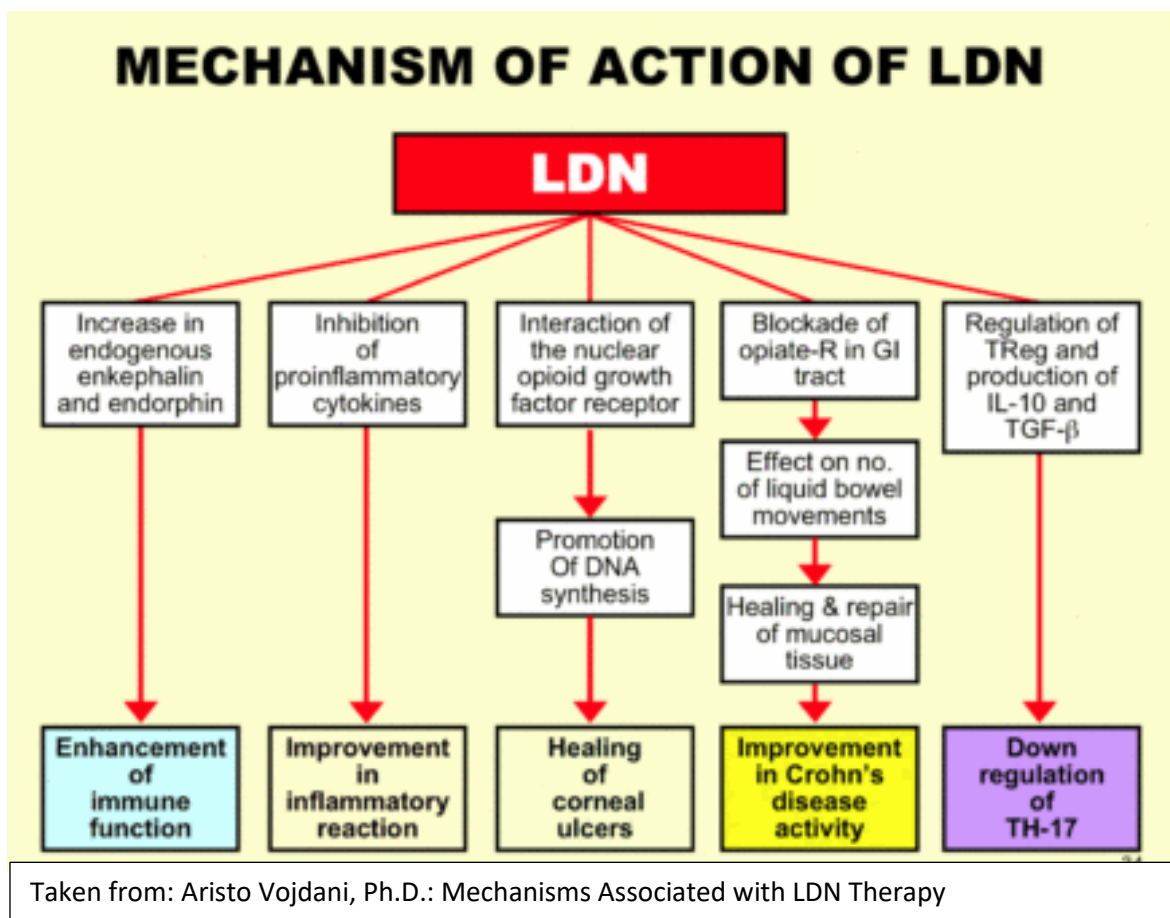
Naltrexone blocks the activation of microglia – immune cells in the central nervous system which are responsible for the release of pro-inflammatory cytokines and neuroinflammation (Younger et al. 2014).

These cells have been implicated in ME/CFS pathology and are also responsible for ‘sickness behaviour’ (fatigue, flu-like symptoms, pain etc.)

The increased endorphin levels also modulate the immune response. It modulates T and B cell production and rebalances the levels of T-helper and T-regulator cells, which are immune cells responsible for stopping the immune system from attacking itself (Bihari 2013).



Microglial Cell.  
Source: Biologend.com



## Evidence to support the use of LDN in chronic diseases

Clinical reports of LDN have demonstrated possible benefits in many chronic diseases such as Fibromyalgia, Sjogren’s syndrome, Crohn's disease, Multiple Sclerosis (MS) and complex-regional pain syndrome (CRPS) (Patten *et al.* 2018).

LDN is a relatively ‘new’ drug to be studied – the first LDN trial in humans was published in 2007. Since then, LDN has been studied in a small number of labs and has been slowly gaining attention as a possible treatment for chronic conditions (Younger et al. 2014).

Case studies, reports and trials demonstrate LDN to be safe and well-tolerated. However, there have been very few large, long-term randomized control trials.

- See the reference list below for other studies using LDN in various diseases.

Two small prospective pilot studies have shown that treatment with LDN may be an effective, safe, and inexpensive treatment for fibromyalgia (Metyas *et al.* 2018).

In a trial of 47 patients with inflammatory bowel disease, LDN resulted in clinical improvement in 75%, and remission in 26% of patients (Lie *et al.* 2018).

LDN has been shown to reduce the need for medication in patients with Rheumatoid Arthritis (Raknes 2019) and it has even been found to improve quality of life in patients with Parkinson’s diseases (Guttuso et al. 2010)

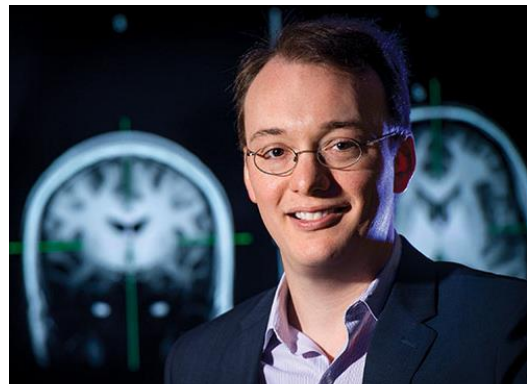
Several studies have found LDN to be a safe, well tolerated and beneficial medication for MS patients (Gironi et al. 2008; Cree et al. 2010; Sharafaddinzadeh et al. 2010).

## Dr Jarred Younger’s work

Dr Jarred Younger in America has done a lot of research into LDN and has conducted successful clinical trials in fibromyalgia (Younger et al. 2014).

In a 2013 placebo-controlled, crossover pilot study involving 31 women with fibromyalgia, LDN reduced daily pain levels, improved mood and quality of life (Younger et al. 2013).

A 2017 study found significant decreases in inflammatory cytokine levels following LDN treatment for 10 weeks in 8 women with fibromyalgia (Parkitny and Younger, 2017).



Dr Jarred Younger. Source: uab.edu

In 2019 he found [evidence of neuroinflammation](#) in ME/CFS, and combined with his theory of microglial cell activation, his team are now also looking into the therapeutic benefits of LDN.

They are currently conducting a [clinical trial](#) for LDN in 30 ME/CFS patients, which is due to be completed in summer 2020, so those results will be very interesting!

# The Australian study of LDN in ME/CFS

## [“Naltrexone Restores Impaired Transient Receptor Potential Melastatin 3 Ion Channel Function in Natural Killer Cells From Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients”](#)

The Australian researchers [previously advanced](#) a hypothesis – which they [validated](#) using their novel ‘patch-clamp’ technology to examine cells – that TRPM3 ion channel function is impaired in natural killer cells (a type of immune cell) in ME/CFS.

Impairment of this ion channel affects calcium signalling, which is needed for effective functioning of natural killer (NK) cells.

Several other studies have also reported abnormalities in Natural Killer cells in ME/CFS.

- In 2018, we produced a summary review of [Natural Killer cell research](#) in ME/CFS.

In this latest study, the researchers investigated the effects of Naltrexone on the activity of the TRPM3 ion channel in NK cells taken from ME/CFS patients.

They isolated NK cells from 8 ME/CFS patients and 8 controls and used their ‘gold standard whole-cell patch-clamp technique’ (which involves running electrical currents through a cell and measuring the change in current) to measure TRPM3 activity, after activation with pregnenolone sulfate.

They then measured TRPM3 activity in NK cells that had been treated with Naltrexone for 24 hours and compared this to those that hadn’t been treated, to observe the changes in ion channel activity and see what affect Naltrexone had on ion channel function.

## Results

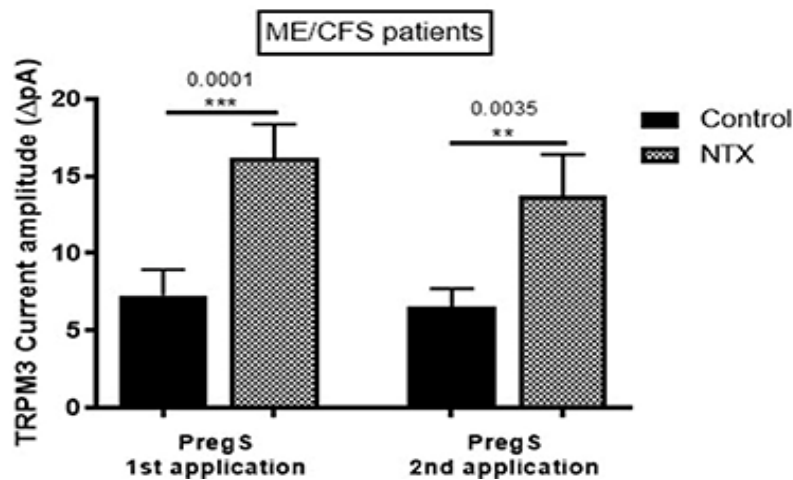
In agreement with their previous studies, the researchers confirmed a “significant loss of the TRPM3 channel activity in CFS/ME patients” after stimulation of NK cells, compared to healthy controls.

“This investigation further helps to establish TRPM3 channels as a prognostic marker and/ or a potential therapeutic target for CFS/ME.”

More importantly, they found that incubation with Naltrexone (NTX) for 24 hours restored TRPM3 channel activity in NK cells from ME/CFS patients, to the same level as healthy controls.

Simply put – the ion channel in the NK cells of ME/CFS patients did not respond to stimulation to the same degree as healthy controls, but after treatment with Naltrexone, the activity of the ion channel was restored to normal levels (See figure 1). This means that the function of the NK cells should also be restored.

“In conclusion, our novel findings indicate that NTX has the potential to restore the TRPM3 channel activity in ME/CFS patients resulting in Ca<sup>2+</sup> signal remodelling, which will in turn affect cell functions, supporting the hypothesis that NTX may have potential for use as a treatment for ME/CFS.”



**Figure 1.** Shows the activity level of the ion channel in NK cells treated with Naltrexone (NTX) (grey bar) vs those not treated with it (black bar) after successive stimulation with Preg S. There is a significant difference between the two- the cells treated with Naltrexone produced a much bigger response when stimulated, showing that Naltrexone has restored ion channel activity.

## Points of concern

- It was a small study – only 8 ME/CFS patients were included. This means that it is hard to draw any conclusions and the study must be repeated in a much larger cohort.
- Laboratory conditions – the study looked at cells taken in isolation, after lots of processing and electric currents were forced through them and various chemicals applied to activate or to inhibit them. This means that it does not reflect conditions inside the body and so it is hard to say whether these results seen in lab conditions would be replicated inside the body.

- Naltrexone dosing – cells were incubated with Naltrexone for 24 hours, something that would not happen when taking the medication in ‘real life’ and it is unclear what actual dose this might reflect in real life.

In order to determine if Naltrexone is safe and of benefit in ME/CFS patients, we need large-scale, long-term clinical trials to be carried out.

## Comment from Dr Charles Shepherd, Hon Medical Adviser, ME Association

“This is a small but interesting laboratory-based research study. However, it would be premature to extrapolate these findings into concluding that naltrexone is likely to be a safe and effective form of drug treatment for ME/CFS.

“We have received very mixed feedback from people here in the UK who have been using naltrexone – even though it is not licensed for treating M.E. Whilst some people report benefits others do not – possibility because naltrexone can produce a number of side effects that overlap with ME/CFS symptoms.

“We have been exploring the possibility of funding a small clinical trial of naltrexone with a researcher in the UK, but no grant application has been received.

“In the absence of any sound evidence of both efficacy and safety, this is not therefore a drug that could be recommended for use in ME/CFS outside a research unit in our current state of knowledge.”

## Conclusion

This latest study demonstrates that Naltrexone may help to correct immune dysfunction at the cellular level and also provides further evidence of natural killer cell abnormalities.

LDN could prove to be a promising therapeutic option to help improve the quality of life of some people. However, large clinical trials are required to test the safety and efficacy of LDN in ME/CFS.

We await the results of Dr Jarred Younger’s clinical trial with anticipation, hoping it will provide further clarity.

### To find out more about Low Dose Naltrexone (LDN):

- [LDN Research Trust](#)
- [LDN Science](#)
- [Health Rising](#)



# The ME Association

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## References

Bihari B (2013) Bernard Bihari, MD: low-dose naltrexone for normalizing immune system function. *Altern Therp Health Med.* 19: 56-65.

Chopra P and Cooper M (2013) Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN) *Journal of Neuroimmune Pharmacology* 8 (3): 470-476.

Conti F, Pittoni V, Sacerdote P, Priori R, Meroni PL, Valesini G. Decreased immunoreactive beta-endorphin in mononuclear leucocytes from patients with chronic fatigue syndrome. *Clin Exp Rheumatol.* (1998) 16:729–32.

Cree BA, et al. (2010) Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Annals of Neurology* 68(2):145-150.

Gironi M, et al. (2008) A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. *Multiple Sclerosis* 14(8):1076-1083.



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Guttuso T et al. (2010) Abstract #13: Low-Dose Naltrexone's Tolerability and Effects in Fatigued Patients with Parkinson's Disease: An Open-Label Study *Neurotherapeutics* 7 (3): 332.

Hammer L et al. (2016) Opioid growth factor and low-dose naltrexone impair central nervous system infiltration by CD4+ T lymphocytes in established experimental autoimmune encephalomyelitis, a model of multiple sclerosis. *Exp Biol Med (Maywood)* 241(1):71-78.

Kariv R et al. (2006) Low-dose naltrexone for the treatment of irritable bowel syndrome: a pilot study. *Dig Dis Sci* 51 (12): 2128-2133.

Ludwig M et al. (2017) P. Serum [Met5]-enkephalin levels are reduced in multiple sclerosis and restored by low-dose naltrexone. *Exp Biol Med (Maywood)* 242(15):1524-1533.

Ludwig MD, et al. (2016) Long-term treatment with low dose naltrexone maintains stable health in patients with multiple sclerosis. *Multiple Sclerosis Journal - Experimental, Translational and Clinical* 2:1-11.

Lie MRKL et al. (2018) Low dose Naltrexone for induction of remission in inflammatory bowel disease patients. *Journal of Translational Medicine* 16 (1): 55.

Metyas S et al. (2018) Low Dose Naltrexone in the Treatment of Fibromyalgia. *Current Rheumatology Reviews* 14 (2): 177-180.

Parkitny L, Younger J. (2017) Reduced pro-inflammatory cytokines after eight weeks of low-dose naltrexone for fibromyalgia. *Biomedicine* 5(2).

Patten DK et al. (2018) The Safety and Efficacy of Low-Dose Naltrexone in the Management of Chronic Pain and Inflammation in Multiple Sclerosis, Fibromyalgia, Crohn's Disease, and Other Chronic Pain Disorders. *Pharmacotherapy* 38 (3): 382-389.

Raknes G (2019) Low dose naltrexone: Effects on medication in rheumatoid and seropositive arthritis. A nationwide register-based controlled quasi-experimental before-after study. *PLoS One* 14 (2).

Ramanathan S et al. (2012) Is fibromyalgia an endocrine/endorphin deficit disorder? Is low dose naltrexone a new treatment option? *Psychosomatics* 53 (6): 591-4.

Ringerike T, Pike E, Nevjar J, Klemp M. (2015) The Use of Naltrexone in Low Doses Beyond the Approved Indication. Oslo: Report from Norwegian Knowledge Centre for the Health Services (NOKC)

Schwaiger T (2018) The Uses of Low-Dose Naltrexone in Clinical Practice: Potential benefits for a wide range of conditions. *Natural Medicine Journal* 10 (4)

- Segal D et al. (2014) Low dose naltrexone for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* (2):CD010410.
- Sharafaddinzadeh N, et al. (2010) The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: a randomized placebo-controlled trial. *Multiple Sclerosis* 16(8):964-969.
- Smith JP et al. (2013) Safety and tolerability of low-dose naltrexone therapy in children with moderate to severe Crohn's disease: a pilot study. *J Clin Gastroenterol* 47(4):339-345.
- Smith JP et al. (2017) Low-dose naltrexone therapy improves active Crohn's disease. *Am J Gastroenterol* 102(4):820-828.
- Sprouse-Blum AS et al. (2010) Understanding endorphins and their importance in pain management. *Hawaii Med J.* 69(3):70-71.
- Toljan K et al. (2018) Low-Dose Naltrexone (LDN)-Review of Therapeutic Utilization. *Medical Science* 6 (4).
- Weinstock LB et al. (2016) Identification and Treatment of New Inflammatory Triggers for Complex Regional Pain Syndrome: Small Intestinal Bacterial Overgrowth and Obstructive Sleep Apnea. *A A Case Reports* 6 (9): 272-276.
- Younger J and Mackey S. (2009) Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. *Pain Med.* 10(4):663-672.
- Younger J et al. (2013) Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis Rheum.* 65(2):529-538.
- Younger J et al. (2014) The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol.* 33(4):451-459.
- Zashin S (2019) Sjogren's Syndrome: Clinical Benefits of Low-dose Naltrexone Therapy. *Curesus* 11 (3).