What is the evidence for low dose naltrexone for the treatment of multiple sclerosis?

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Date prepared: 05/02/2020

Background

Naltrexone is licensed in the UK as an adjunctive prophylactic treatment in the maintenance of detoxified, formerly opioid dependent patients. Its use is usually initiated in specialist clinics with a typical dose being 50mg orally daily (1, 2). Naltrexone in combination with bupropion is licensed as an adjunct for the management of weight in clinically obese adult patients (3). When used to treat multiple sclerosis (MS), typically doses of 3 to 4.5mg daily are taken; hence the term low-dose naltrexone (LDN) (4, 5).

The use of LDN for immunomodulation was developed and promoted by Dr Bernard Bihari, a neurophysician in the United States. LDN has been in use in the United States for treatment of MS since 1985. There is not a commercially available LDN product and therefore either capsules or a liquid preparation have to be specially prepared (4). LDN therapy is therefore an unlicensed treatment in the UK (4, 5).

It is claimed that LDN in MS patients can significantly improve mood, spasm, fatigue and pain (4). In view of the above, the actual evidence to support the use of LDN for MS needs to be clarified.

Answer

Research suggests that LDN acts by stimulating production of endorphins (natural pain killers) which in turn stimulates the immune system (4). Conventional MS treatment aims to suppress the immune system (6).

The first published clinical trial of LDN use in MS was presented in 2008 (7). 40 adult Italian patients with a definite diagnosis of primary progressive MS were enrolled in an open, uncontrolled, 6 month study to assess safety and tolerability of LDN. Efficacy was assessed as a secondary outcome. Patients were included if they had been diagnosed with MS longer than 2 years, had stable disease for the past 6 months and were affected by spasticity, pain, fatigue and/or depression defined by scores on various assessment scales. Patients were excluded if they were treated with concomitant opioids at the time of inclusion. Patients were commenced on an oral dose of 2mg at bedtime which was then increased to 4mg within the first 2 weeks and continued until the end of the study. Scheduled follow up visits occurred 1, 3 and 6 months after the beginning of LDN treatment and 1 month after the end of the study. The follow up visits assessed disease progression and adverse effects. 35 patients completed 6 months of therapy. 3 patients stopped due to adverse effects, 1 stopped due to disease progression and 1 stopped because they took an opioid containing medicine to treat pain.

27 patients experienced at least 1 adverse effect. 95% of adverse effects were classed as minor. One third of adverse events were haematological abnormalities – increases in bilirubin, liver enzymes and cholesterol levels were noted and some patients had leucopenia. Other adverse effects included urinary tract infections, mild agitation and sleep disturbance.

During the 6 month study, spasticity was improved in 47.4% of patients, worsened in 10.5% of patients and remained stable in 42.1%. The improvement in spasticity was statistically significant (p=0.008). Depression was improved in 55.6% of patients and worsened in 33.3%. Fatigue improved in 33.3% of patients and worsened in 41%. There was a statistically significant increase in pain with 56.4% of patients experiencing worse pain compared to 28.2% having improved pain. No statistically significant improvement in quality of life was noted. The authors conclude that the data indicates that

LDN is a relatively safe and well tolerated drug in patients with primary progressive MS. However, a randomised, double blind, placebo controlled trial needs to be performed to fully assess the efficacy and safety of the drug. (7)

Two similar, short-term, crossover studies published in 2010 reported differing results – one study found no beneficial effects (8) whereas the other found that LDN had no effect on physical functioning but did improve pain and mental health (9).

A 17-week randomized, double-blind, placebo-controlled, parallel-group, crossover-design clinical trial was conducted in two universities in Iran (8). A total of 106 adult patients aged between 15 and 65 years who had relapsing–remitting MS (RRMS) or secondary progressive MS (SPMS) for longer than 6 months were enrolled into the study. Patients were included if they were not taking disease modifying drugs before the study and they were able to take medication for at least 3 months without changing or discontinuing it. Exclusion criteria were use of opioid analgesics or immunosuppressive drugs (e.g. cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, natalizumab, rituximab and alemtuzumab). The patients were split into 2 groups - 53 patients were assigned to take LDN 4.5mg at night (between 9pm and 3am) for 8 weeks and then after a 1 week washout period, switch to placebo for 8 weeks. The other 53 patients did the opposite by starting with placebo and switching to LDN.

Data on physical and mental health before, during and after the trial were collected through patient questionnaires. The primary outcome of the study was comparison of physical and mental health scores by conducting independent t-test of the results obtained in the middle and at the end of study between the two groups. 96 patients finished the study. Variables including presence of pain, energy, emotional well-being, social, cognitive, and sexual functions, role limitation due to physical and emotional problems, health distress, and overall quality of life did not show any statistically significant difference between the two groups. Factor analysis revealed that health perception scores were statistically different between the groups before starting, in the middle, and at the end of the study. The authors conclude that the study clearly illustrates that LDN is a relatively safe therapeutic option in RRMS and SPMS, but its efficacy is under question and probably a long duration trial is needed in the future. (8)

A single centre, double-masked, placebo-controlled, crossover study evaluated the efficacy of treatment with 4.5mg LDN taken at night on self-reported quality of life, in adult patients with any type of MS (9). 80 subjects with clinically definite MS enrolled in the 17 week trial. Participants had to be willing to not change or start disease-modifying or symptomatic therapies for the duration of the trial. Patients currently treated with interferon (IFN) β (either IFNβ-1b or IFNβ-1a) or glatiramer acetate (GA), or not on disease modifying therapy, were allowed entry into the trial. Exclusion criteria included starting a disease-modifying therapy within the past 3 months, receiving long term treatment with opioid analgesics, concurrent use of both IFNβ and GA, and taking immunosuppressive medications including natalizumab. Quality of life was assessed using the Multiple Sclerosis Quality of Life Inventory (MSQLI). Patients were treated with either LDN or placebo for 8 weeks, followed by a 1-week washout, followed by 8 weeks of treatment with the alternate study drug. All subjects received 8 weeks of treatment with both LDN and placebo, in either order, and were masked as to the order of treatment. The MSQLI was completed before the study drugs were started, then following each 8 week period of drug administration. 70 patients completed both treatment periods (10 patients withdrew from the study); but only 60 patients completed all 3 required MSQLIs. The lack of data for 25% of the enrolled participants substantially reduced the statistical power of the trial.

The results from the MSQLI showed that 8 weeks treatment with LDN significantly improved quality of life measures specific to mental health. There was a 3.3 point improvement on the mental component summary score of the Short Form-36 General Health Survey ($p=0.04$), a 6 point improvement on the mental health improvement scale ($p<0.01$), a 1.6 point improvement on the Pain Effects Scale ($p=0.04$) and a 2.4 point improvement on the Perceived Deficits Questionnaire. The order of treatment

with LDN or placebo did not influence the results. There was no impact on the quality of life measures specific to physical health. The study authors state that this is to be expected because of the short duration of treatment. LDN was well tolerated during the study, no relapses were reported during the 17 weeks and no serious adverse events were reported. Adverse events that did occur were vivid dreams, fatigue, flu-like symptoms, insomnia, loss of appetite and sinus infection. (9)

Cree et al concluded that the results do not support use of LDN as an alternate to proven MS treatments such as IFNβ, GA, and natalizumab. The study did not find any evidence of incompatibility between LDN and IFNβ. Confirmation of the study findings in a multicentre trial will be necessary to reach definite conclusions about the possible symptomatic benefit of LDN in MS. A longer duration of treatment is also necessary to determine whether LDN has any benefit with respect to physical outcome measures. (9)

The long term use of LDN has not been studied and evaluated by a clinical trial (5). A retrospective chart analysis of 215 adult MS patients attending an MS clinic prescribed 3.5mg LDN, mainly for fatigue, published in October 2015 showed that mean duration of exposure to LDN was 817 (standard deviation (SD) 512) days and the median period of treatment was 804 days (10). One hundred and eleven patients who discontinued LDN because of insomnia, nightmares, no improvement in fatigue and recurrence of MS flares, received the drug for a mean of 526 days. Individuals who continued on LDN were on the drug for a mean of 1217 (SD 414) days and a median of 1254 days. LDN was taken by 152 women and 63 men and >75% had RRMS, with a mean duration of 10 years. Of the 215 patients, 128 (60%) reported a reduction in fatigue, 50 experienced no change and 4 stated there was an increase in fatigue. One hundred and thirty patients felt their MS had stabilised or improved while on LDN and 75% of patients reported improved or stabilised quality of life. The authors conclude that the data support future prospective double blind investigations.

Another retrospective chart analysis of 54 adult RRMS patients attending a MS clinic over 10 years was published in September 2016 (11). Patients were treated with 3, 3.5 or 4mg LDN with or without concomitant GA. The average duration of exposure to LDN was 1095 days for the LDN only cohort, and 1418 days for the LDN-GA cohort. All patients in both cohorts remained on LDN therapy throughout the duration of the study. 1 patient in the LDN cohort experienced multiple reported flares, whereas 6 patients from the LDN-GA cohort had multiple flares during the course of the study. The remaining patients all had a singular flare during the course of the study. Evaluation of clinical laboratory blood values, behavioural data and interpretation of MRI revealed that treatment of patients with RRMS who received LDN was associated with no significant adverse effects. Disease status did not progress with LDN monotherapy in comparison to data obtained from the LDN-GA cohort. The Authors conclude that study illustrates that LDN is safe for people with MS and the efficacy of LDN needs to be evaluated in prospective clinical studies of MS.

There have been reviews of the literature published over the past several years. One review of complementary and alternative medicines used in MS published in 2014 (12) states that the published data from a randomised controlled trial and cross over study are inadequate to support or refute the use of LDN for improving quality of life and both studies were underpowered to exclude a meaningful clinical effect (8, 9).

Two more recent reviews were published in 2018 (13, 14). The papers discussed in these reviews are the ones that have been summarised above. Both these reviews reached the same conclusion that, although there is some promise in LDN for MS, the current evidence base is insufficient to recommend its use in routine practice. Sufficiently sized randomised controlled trials are necessary to draw firm conclusions on the efficacy of LDN for MS. However, there is little incentive for pharmaceutical companies to conduct this research as naltrexone is inexpensive and off-patent.

LDN should not be used at the same time as morphine treatment or a derivative of morphine. On starting LDN the recent use of opiate analgesics will result in an opiate withdrawal syndrome with

increased pain, muscle spasm and possible vomiting and diarrhoea (4, 8). It is therefore advisable that any opiate analgesics be discontinued at least two weeks before starting LDN (4).

There is limited information in the published clinical trials about other medicines patients were taking. In the studies conducted to date, patients on opiates were excluded (7-11). Two of the trials excluded patients taking immunosuppressive medicines including natalizumab (8, 9). One study excluded patients who took both IFNβ and GA, however if they were taking either IFNβ or GA they were included. No evidence of incompatibility between LDN and IFNβ was noted (9). In the retrospective chart reviews, some patients took LDN as well as immunosuppressive treatment; no interactions were reported (10). MS-UK states that LDN is compatible with steroids and MS disease modifying drugs (4).

The Multiple Sclerosis Society states that 'There is virtually no published clinical evidence to support the use of LDN in MS. What evidence exists is small scale, pilot exploratory phase I studies, which are conflicting, and do not include adequate end points. No dose ranging or long term full scale confirmatory studies have been carried out. A repeat of the pilot studies should be considered before any further work is done, and/or there is a need to define what would constitute a reasonable "proof of concept" for phase II studies'. (5)

Summary

- Small pilot studies have shown that LDN is a relatively safe and well tolerated drug in people with MS and can improve some symptoms.
- A retrospective review of the long term efficacy and safety of LDN showed that 60% of patients reported a reduction in fatigue and stabilised/improved MS.
- One study did not find any evidence of incompatibility between LDN and IFNβ. LDN may block the analgesic effects of opioid drugs and they should not be used together.
- If LDN is used to treat MS, both the indication and product formulation are unlicensed.
- The current data is inadequate to support or refute the use of LDN for improving MS symptoms and quality of life. A randomised, double-blind, placebo-controlled trial needs to be performed to fully assess the efficacy and safety of the drug.

Limitations

It is difficult to satisfactorily comment on the efficacy and safety of a product when there are only a few clinical trials. Information presented mainly on websites is not subject to peer review.

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Quality Assurance

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Date Prepared
05/02/2020

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Date of check
11/02/2020

Search strategy
- BNF online, electronic Medicines Compendium, Martindale, AHFS DI online, DrugDex, Cochrane Library, PubMed, NICE Evidence, UpToDate: search terms = naltrexone + multiple sclerosis
- Embase, 1974 to date, search terms = NALTREXONE/ AND MULTIPLE SCLEROSIS/dt [dt=Drug Therapy] [Limit to: Human and English Language and Publication Year 2018-Current]
- Medline, 1946 to date, search terms = NALTREXONE/ AND MULTIPLE SCLEROSIS/dt [dt=Drug Therapy] [Limit to: English Language and Humans and Publication Year 2018-Current]
- Internet websites - http://www.mssociety.org.uk, http://www.ms-uk.org