Low Dose Naltrexone (LDN) – a review of the clinical trial evidence

Summary

There is considerable interest in the possibility that naltrexone is effective when given in low doses for the treatment of Multiple Sclerosis. Naltrexone is normally used at higher doses in the treatment of heroin addiction. Because of this interest the MS society has reviewed the clinical trial data that has been published on LDN; to look at what published clinical trial evidence currently exists to support the drug’s use in Multiple Sclerosis.

Three clinical trials have been published. These are only exploratory (pilot) early studies at this stage and the evidence they provide is limited. Two of the studies (1) (2) compared LDN’s effectiveness against placebo; the third trial was a small scale study which only looked at safety (3). There are a number of issues with these studies, even as pilot investigations:

- For a chronic condition like MS patients need to be treated longer in clinical trials – even at the pilot stage.
- The placebo comparison study results are conflicting - one study found that there was no difference between LDN and placebo, and the other showed some effects, which were borderline because of problems with the data in the study.
- The effects seen were only on some measurements of “quality of life” – more important tests of clinical benefit on disability, disease progression or specific symptoms have not been done in placebo studies.
- No work has been done to test that the dose recommended for LDN is the best dose to use – normally a range of doses are tested in early clinical trials.
- Clinical trials need to be targeted according to whether LDN is considered to be a disease modifying agent or a treatment for specific symptoms, and according to specific types of MS, e.g. relapsing remitting or primary progressive.

Without a marketing authorisation from the regulatory agencies, products can only be prescribed on a ‘named patient’ basis and cannot be marketed or promoted. For an MS product pilot studies would have to be followed by large scale, long term (over 2 years for disease modifying drugs) placebo controlled confirmatory clinical trials in large numbers of patients (of the order of 1500 or more), including safety data.
New and extended pilot studies are needed to provide better evidence that LDN is a good candidate for MS treatment with potential for approval by the authorities. If new pilot data were encouraging an extensive clinical programme would be required for the development of LDN to the stage of Regulatory Approval. This would be likely to be some years away and there are concerns about finding the large investment to fund such a programme. Without this evidence and resulting approval there is no opportunity for LDN to be available on general prescription in the UK in the near term.

References:
N Sharafaddinzadeh et al
Mult Scler 2010 16:964

(2) Pilot trial of low dose naltrexone and quality of life in multiple sclerosis
B A C Cree, et al
Ann Neurol 2010 68:145-150

(3) A Pilot trial of low-dose naltrexone in primary progressive multiple sclerosis
M Gironi et al
Mult Scler 2008 14:1076
Low Dose Naltrexone (LDN) – a review of the clinical trial evidence

Full report

Introduction
This report is based on papers from a literature search conducted on 17 January 2011. The search strategy covered three on-line databases, PUBMED, TRIPS and the Cochrane Reviews database, using the search terms “Low Dose Naltrexone” AND “Multiple Sclerosis”. Pre-clinical reports and reviews/commentaries have not been included in this summary, which only includes clinical trials. Individual published case reports would have been included if they had been found. A number of International conferences and one European conference have been held, which only included anecdotal data and patient surveys in addition to the clinical trials summarised here.

Clinical Pharmacology and Pharmacokinetics studies
No clinical pharmacology or pharmacokinetics studies of LDN were found.

Number and type of Clinical Trials
Three clinical trials are reported in the literature – all are small scale exploratory pilot studies:


M Gironi et al: A Pilot trial of low-dose naltrexone in primary progressive multiple sclerosis

Design of Clinical Efficacy Studies
Two of the studies were conducted to the same design (Sharafaddinzadeh & Cree):

Randomised double blind placebo controlled cross over studies of 17 weeks duration. Each treatment arm (A or B) of the study comprised two 8 weeks treatment phases separated by a 1 week washout at the crossover point. In Arm A patients were first treated with placebo, in arm B patients were first treated with LDN, crossing over to the alternative treatment. Assessments were made at start, at the crossover, and at the end of treatment.

The 3rd study (Gironi) was open and uncontrolled, intended as a pilot safety study.

Dose and Duration of Treatment
All studies were oral dosing.

Sharafaddinzadeh & Cree both studied an 8 weeks treatment duration in a crossover design. Cree used a 4.5 mg nightly dose; the dose was not specified in the Sharafaddinzadeh study

December 2011
Gironi’s study dosed at 2 mg for 4 weeks, increased up to 4mg if required after 2 weeks, with an overall duration of treatment of 6 months.

No dose ranging studies to support the dose used in these studies were found.

**Test products**
Cree: capsules locally compounded.

Sharafaddinzadeh & Gironi: formulation not specified

**Selection Criteria**
Selection criteria varied in the three studies, Studies have not been done, as recommended by the CHMP guidelines, separately in the specific MS diagnoses groups (Relapsing Remitting – RRMS; Secondary Progressive – SPMS; Primary Progressive – PPRMS; and Progressive Relapsing – PRMS).

In the double blind studies:

Cree: Clinically definite MS, across all forms of disease RRMS, SPMS, PPMS, PRMS, (most patients had RRMS). Current Interferon of Glatiramer treatment could be continued (unless it had started less than three months pre-study), and patients not on disease modifying therapy could be included. The main exclusions were: patients on opiate agonists, LDN or on both Glatiramer or Interferon, on immunosuppressants including natalizumab, and exclusions were related to inability to complete the questionnaire.

Sharafaddinzadeh: “Clinically definite” relapsing remitting or secondary progressive MS of at least 6 months duration, not treated with disease modifying drugs or other MS medications during study. Expanded Disability Status Scale (EDSS) measurements were made at each visit, to categorise disease status as mild, moderate or severe. 52% were mild, 31% moderate 17% severe across both groups – evenly distributed in the groups (not statistically significant). EDSS comparisons between placebo and active groups during the trial were not part of the efficacy assessment criteria, most patients were mildly affected by their MS.

Both the double blind studies used the McDonald/International Panel criteria.

In Gironi’s open study:

Primary progressive MS according to McDonald Criteria. EDSS between 3.0 and 6.5, & disease duration longer than 2 years; stable in previous 6 months. Presence of at least one physical symptom, fatigue or depression at a pre-defined level was required. Concomitant medication exclusions were defined. Disease progression based on disability levels (EDSS) was measured. Gironi’s patients had a mean disease duration of 12.7 +/- 6.8 year and a Median EDSS of 6 (3-6.5).

**Numbers of Patients and Diagnoses - Withdrawals**
A total of 226 patients have been enrolled in LDN pilot studies of whom 201 completed the studies.

December 2011
Sharafaddinzadeh enrolled 106 patients of whom 8 withdrew due to lack of efficacy and 2 due to lack of completion of questionnaire 96 (50Placebo & 46LDN) completed the study. All had RRMS or SPMS – but patient numbers with each separate diagnosis were not specified.

Cree enrolled 80 patients with clinically definite MS (International Panel Criteria), across all forms of disease RRMS, SPMS, PPMS, PRMS, (numbers were reported, mostly RRMS. 10 patients withdrew: 8 for personal reasons, 1 (placebo) withdrew due to perceived efficacy, 1 withdrew due to an underlying medical condition. There were incomplete data in 10 subjects.

Gironi enrolled 40 patients: 35 completed and 5 terminated prematurely (reasons stated).

**Assessment Criteria – Efficacy**
Both the placebo controlled studies only assessed quality of life according to different questionnaires – Sharafaddinzadeh used MSQOL-54, Cree used the Multiple Sclerosis Quality of Life Inventory. Quality of life questionnaires were completed by the patients at baseline and at end of each treatment period (ie after 8 weeks on LDN and 8 Weeks on placebo). Disability score (EDSS) was not assessed after treatment.

In the open study (Gironi) efficacy variables were secondary to the safety variables: The secondary efficacy outcomes in this study were: fatigue (FSS), pain (VAS), spasticity (Modified Ashworth), and depression (Beck Depression Inventory) (rating Scale). The study also included a Quality of Life questionnaire. (Italian validated version of SF-36). Assessments were at 1, 3 and 6 months treatment and 1 month post treatment.

**Assessment Criteria – Safety**
All studies included adverse event monitoring, in addition Sharafaddinzadeh covered patient history, physical/neurological examination, at each visit. Gironi’s study was intended as a safety study with the following as primary outcomes: patient history, physical/neurological examination, vital signs, adverse events, blood biochemistry and urinalysis.

**Results – Efficacy**
In Cree’s study in 80 patients statistically significant differences in mental health QOL measures were observed for LDN compared to placebo, according to a per protocol analysis. Improvements were reported in: Mental Component summary score of the short form-36 general health survey (3.3 points p= 0.04); Mental health Inventory (6 points p>0.01); Pain Effects Scale (1.6 points p=0.04); Perceived deficits questionnaire (2.4 points P= 0.05). However statistical significance was lost when an intent to treat analysis was done. No effects were observed on any of the physical QOL indices, drop-outs (10 patients) and data management errors (10 patients) substantially weakened the statistical power of the study.

In Sharafaddinzadeh’s study of the same placebo controlled crossover design in 106 patients there was no statistical difference in Quality of Life scores between the
placebo or active treated groups at any of the assessments after 8 weeks of treatment.

Gironi’s study is limited as far as efficacy assessment is concerned as an open study with efficacy as secondary variables, and employing subjective rating scales with no placebo group. However the following observations were made: a reduction in spasticity (modified Ashworth scale) compared to baseline, at all treatment visits, and an increase in pain score (VAS). No changes in fatigue or depression scores, or quality of life scores were reported.

In Gironi’s study Basal Endorphin levels were significantly increased at 3 and 6 months. There was no association between mRNA levels and allelic variants of the u opioid receptor gene and improvements in spasticity.

**Results – Safety**

Sharafaddinzadeh: Adverse events were minor, categorised as not interfering with function or daily living activities. Main recorded adverse events were nausea, epigastric pain, mood alteration, mild irritability, headache, joint pain (incidence not specified).

Cree: No serious ADRs were reported, vivid dreaming was reported in 7 placebo and 10 LDN patients and thought to be potentially treatment related. Other ADEs reported were: fatigue (2 Placebo – 1 LDN) Flu (1 Placebo) insomnia (1 Placebo) loss of appetite (1 LDN) sinus infection (1 LDN).

Gironi’s study was intended as a pilot evaluation of safety: Adverse events were reported in 27/40 (67.5%) patients entered. 2 ADE were rated severe or life threatening (1 urinary infection causing renal failure not requiring dialysis, 1 bone metastases presenting lung carcinoma – not considered by the investigator to be treatment related. Other ADEs were rated as not interfering with function or not interfering with daily living activities (using the Common Terminology Criteria for Adverse events). Neurological Disability was assessed by EDSS, with the following results: progression of disease in 1 patient, unchanged in 35, and improved in 3 (1 patient lost to follow up), which according to the investigator was attributable to natural history of disease.
Evaluation of Clinical Studies

These studies are discussed with reference to the Committee for Medicinal Products for Human Use guideline on the clinical investigation of medicinal products for the treatment of multiple sclerosis – the “CHMP guideline”. This sets out the requirements for clinical evidence to be submitted for Marketing Authorisation in the European Union, covering both the European Medicines Agency (EMEA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA).

All the studies were small scale, pilot exploratory studies, relating to clinical research phase I; no dose ranging or proof of concept studies or long-term full scale confirmatory studies have been carried out.

The two placebo controlled efficacy studies were of 8 weeks duration, whereas the CHMP guideline expects a duration of 6 months for exploratory placebo controlled studies in MS. All the studies used only quality of life rating scales as the assessment criteria, however the CHMP guideline refers to the use of MRI scanning as a useful end-point in exploratory studies and requires that relapses, disability, and other meaningful clinical outcomes should also be evaluated. The CHMP guideline also refers to the need to consider additional markers of disease activity across the drug development programme. Longer durations than 8 weeks would be required to see evidence of effects on physical functioning in MS, or on indicators of disease progression.

As far as quality of life assessments are concerned the evidence consists of one borderline positive pilot study in some mainly mental health quality of life parameters and one negative pilot study, both to the same placebo controlled cross-over design. EDSS measurements of disability were made but were not reported as efficacy outcomes in these two studies.

The available data are not convincing as pilot studies, and may not on their own encourage the progression to more extensive phase 2 as a preliminary to the large scale confirmatory studies required for regulatory approval. The goal of treatment with LDN is not clear from the available clinical data. It is not clear if it is a potential disease modifying treatment or a potential symptomatic treatment for MS, although very preliminary data exists on improvement in symptoms of spasm from the Gironi open study in a few patients. Some animal pharmacology data exists, but this is not included in this review. Gironi showed some effects on endorphin levels and spasticity which may suggest assessment of symptomatic improvements as a likely goal for any further pilot studies.

Quality of life assessment, employed in the LDN studies, is considered the least relevant of the criteria available for assessment in Multiple Sclerosis trials, since according to the CHMP guideline few data are available on validation of specific instruments for Quality of Life assessments in MS. For Marketing Authorisation the expectation is that efficacy assessments will include end points related to clinical benefit. Examples might be: prevention or delay of disability progression, relapse rate (if relevant to the indication), MRI scanning, other disease progression indicators and means of defining progression of disability such as neurological rating scales, cognitive impairment, fatigue scales, ambulatory index, or validated rating scales for symptomatic improvement claims. Clinically relevant benefit and statistical

December 2011
significance compared to placebo are required. None of these key types of end-points were evaluated in the two placebo controlled studies. Clinical end points data was collected in Gironi’s study, but this was open, uncontrolled and these were secondary to the primary objective of evaluating safety.

Longer duration of treatment & specific assessment criteria are needed to define efficacy of LDN.

De Cree’s study selected and evaluated patients with all forms of MS, however clinical trials assessments are expected to differentiate between the various clinical patterns of MS for example distinguishing between primary progressive and the other forms of MS.

The licenced dose for naltrexone treatment of heroin addiction in the UK is an initial oral dose of 25 mg (half a tablet) followed by 50 mg (one tablet) daily. At a lower dose its opiate antagonist activity has been postulated to switch to an agonist effect to trigger prolonged release of endogenous opioids such as Beta endorphins (ref 2 - Gironi). Such a low dose regimen (as devised by Bihari) is commonly recommended if naltrexone is prescribed for MS:

1.5mg as liquid for 2 weeks increasing by 0.5mg every 2 weeks until individual finds dose that suits them best. Increasing symptoms might indicate that the dose is too high – lower the dose and improvements should become apparent (From the LDN research trust web site information pack [http://www.ldnresearchtrustfiles.co.uk/docs/LDN%20Information%20Pack(1).pdf](http://www.ldnresearchtrustfiles.co.uk/docs/LDN%20Information%20Pack(1).pdf))

No dose ranging studies to justify the commonly recommended regimen and no clinical trials with the commonly recommended regimen have been found.

The available data on LDN may be set in context with the extent of data expected for Marketing Authorisation by reference to the CHMP Guideline and regulatory agency evaluation reports for TYSABRI (a disease modifying agent), and SATIVEX (for the treatment of spasm), with some of the key points listed in outline below:

- Selection of sufficient patients separately for the various subgroups of MS.
- Double blind randomised parallel group comparisons with placebo and reference active comparator medication (where relevant eg vs corticosteroids in acute relapses)
- Considerably more extensive evaluation of clinically relevant end-points, including all appropriate clinically relevant outcome measures (eg disability progression, relapse rates, MRI Scanning, validated rating scales or specific symptom scoring such as spasticity); with trials planned according to defined goals of therapy for LDN.
- Large scale long term studies, usually in replicate.
- A minimal data base would be 1500 patients.
- For MS disease modifying indications 2 years treatment in a meaningful number of patients is expected, with a number of particular MS specific parameters to be followed up long-term.
Further data on pharmacology, mechanism of action and pharmacokinetics is likely to be required.

The Tysabri data package first submitted for approval comprised three phase II studies and two pivotal confirmatory phase III trials, all double blind comparisons with placebo. Over 1500 Tysabri treated patients were included, the majority for 2 years treatment in the pivotal trials. The indication studied was relapsing remitting MS as defined by McDonald Criteria, with relapse rates, MRI, EDSS and functional rating scale endpoints. Tysabri is approved for single disease modifying therapy in highly active relapsing remitting multiple sclerosis in specific patient groups.

The CHMP guideline focuses specifically on disease modification and improvement of disability, and does not cover requirements for symptomatic treatment

Sativex’s approved indications are symptomatic in nature, although quite limited. Sativex is approved for add-on therapy for symptomatic relief of spasticity unresponsive to other treatments, after a trial period of Sativex treatment. The data package on which approval was based included over 1500 patients treated for up to 19 weeks in two phase II dose response studies and four phase III confirmatory placebo controlled efficacy trials. There were 3 other smaller phase III studies one with a duration of treatment of up to 3.5 years in 36 patients. Assessment criteria were rating scales for spasticity (critical attention was paid to the validity of the rating scales in the regulatory review). There is no indication for disease modifying effects since evidence was not provided in the application.

This summary has not considered the availability of the data that would be required on preclinical studies (pharmacology, toxicology, carcinogenicity and reproduction studies) or on pharmaceutical dose form development, stability and manufacturing. It is believed that formulations used at present are manufactured on pilot scale. Some relevant data may be on file with the current manufacturers of naltrexone products, or at the regulatory agencies.

Conclusion
There is virtually no published clinical evidence to support the use of LDN in Multiple Sclerosis. What evidence exists is exploratory, conflicting, and does not include adequate end points. Repeat of the pilot studies should be considered before any further work was done, and/or there is a need to define what would constitute a reasonable “proof of concept” for phase II studies.

An extensive clinical programme would be required for the development of LDN to the stage of Regulatory Approval, especially if a disease modifying indication is sought, although the requirements for a limited symptomatic indication in spasticity may be less in terms of study durations a full development programme would still be required. Even if there was convincing exploratory or concept data a Marketing Authorisation Application would be some years away.

The cost/price of LDN is low, of the order of £1.30 per tablet (pharmacy web-sites) and could be a barrier to finding the investment necessary to develop LDN for use in MS, if adequate pilot data could be obtained.

December 2011
References:
A Pilot trial of low-dose naltrexone in primary progressive multiple sclerosis
M Gironi et al
Mult Scler 2008 14:1076

N Sharafaddinzadeh et al
Mult Scler 2010 16:964

Pilot trial of low dose naltrexone and quality of life in multiple sclerosis
B A C Cree, et al
Ann Neurol 2010 68:145-150


Tysabri, European Public Assessment Report
Accessed from the European medicines Evaluation agency web-site March 2011

Sativex Public Assessment Report, Concerptation Procedure
Accessed from the UK Medicinal and Healthcare products Regulatory Agency web-site March 2011
http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf

Note: A further clinical trial is referred to on an LDN web-site, www.lowdosenaltrexone.org conducted by Dr Evers in Sundern Germany, but a report could not be found.