ATTACHMENT 8.

Submission for NHS Surrey Area Prescribing Committee
Treatment: Low dose naltrexone for MS
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1. Purpose of the Review

£23,135 was spent on low dose naltrexone (LDN) within NHS Surrey in the last year. Ancedotal reports claim that LDN is able to enhance the immune system, reduce or stop disease progression, reduce muscle spasm, fatigue, improve bladder control, mobility, pain et cetera in patients suffering from Multiple Sclerosis (MS). This document reviews the evidence for LDN for MS.

2. Appropriateness

2.1 The patient: Patients experiencing symptoms of MS despite treatment on conventional licensed treatments for MS or patients reluctant to take conventional treatments as they have been informed that they are toxic or ineffective[1].

2.2 The problem: LDN is unlicensed in MS and requires ordering as a "specials" product which represents a significant cost. The Multiple Sclerosis Resource Centre, a charity which provides information to individuals suffering from MS has produced an information pack on LDN which advises: *unfortunately, thus far, many GP's and Neurologists seem unwilling to prescribe LDN as they have little experience or knowledge of Naltrexone being used in this way at such a low dosage for the treatment of MS symptoms.The enclosed pack has been formulated in order to provide your GP or Neurologist with the information they need to be able to consider prescribing you with LDN on an NHS Script. This can be done on an "off licence" basis (sometimes referred to as "off label")* [1].

Definition: Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS).[2] MS lesions, characterized by perivascular infiltration of monocytes and lymphocytes, appear as indurated areas in pathologic specimens; hence, the term sclerosis in plaques.

Effects and prognosis: MS is a dynamic disease, with almost constant lesion formation and a progressive clinical course leading to physical disability[2]. For every 8-10 new lesions detected on magnetic resonance imaging (MRI), only one clinical manifestation typically can be demonstrated. Patients with relapsing remitting MS have an average of 5-10 new lesions per year and 1 or 2 clinical exacerbations.[2]

Multiple sclerosis causes considerable disability in the working age group.[2] People with MS usually die of complications rather than of MS itself, including recurrent infections (especially in bedridden patients).[2] Patients with MS are thought to have an average life expectancy 5-7 years shorter than that of the general population.[2]

Etiology: Despite intensive efforts in finding the source of the disease, no etiologic agent for MS has been identified[2]. Some experts argue that MS could be a

heterogeneous disorder triggered or perpetuated by several different environmental agents.[2]

Diagnosis: There is no single specific diagnostic test available, but in practice, the diagnosis can be made clinically in most people after excluding other neurological disorders.[3] In 2001 the International Panel on MS Diagnosis published revised diagnostic criteria for MS (McDonald criteria).[4] These criteria focus on the objective demonstration of dissemination of lesions in both time and space.[4] Magnetic resonance imaging is integrated with clinical and other para-clinical diagnostic methods.[4] The outcome of a diagnostic evaluation is either MS, "possible MS" (for those at risk for MS, but for whom diagnostic evaluation is equivocal), or "not MS."[4]

The Expanded Disability Status Scale (EDSS) is used as one of the criteria for eligibility via the DoH risk sharing scheme.[5] EDSS steps 1.0-4.5 refer to patients with MS who are fully ambulatory.[5] EDSS steps 5.0-9.0 are defined by the impairment to ambulation.[5]

2.3 The Intervention: Naltrexone is licensed as an adjunctive prophylactic therapy in the maintenance of detoxified, formerly opioid-dependent patients at a dose of 50mg daily[6].

How does it work: Naltrexone is a specific, high affinity, long acting competitive antagonist at opioid receptors. It has negligible opioid agonist activity[6].
Some research suggests that when naltrexone is given at low doses it triggers a prolonged up-regulation of endorphins. This increase may have an anti-inflammatory effect which could be beneficial in the treatment of MS. It has also been hypothesised that LDN may be able to reduce injury to the nervous system by decreasing the harmful effects of free radicals and excitotoxins[13]

Care setting: Primary care and secondary care

Frequency: For MS, the usual dose of LDN is 4.5mg each day, taken late each evening[1].

2.4 Alternative treatments: There are a wide range of treatments for MS including the disease modifying treatments (DMTs): beta-interferon-1a (Avonex® and Rebif®), beta-interferon-1b (Betaferon®) glatiramer acetate (Copaxone®). Natalizumab (Tysabri®) has different criteria for use and is reserved for rapidly evolving severe relapsing-remitting MS.

One of the proposed mechanisms of action of LDN is to boost the immune system whereas conventional MS treatment aims to suppress the immune system. There is concern that LDN treatment may actually have the opposite effect than that demonstrated by standard MS therapy[1, 13].

Therefore, advocates for the use of LDN do not recommended its use in conjunction with other immunosuppressant drugs (e.g. corticosteroids, beta-interferon, methotrexate, and azathioprine). This may not be a realistic option for many MS patients and it would be unwise to stop an approved licensed treatment in order to take LDN. LDN may also block the analgesic effects of opioid drugs. [1] It is therefore prudent to avoid LDN in those MS patients who need opioids for chronic pain.

3. Effectiveness

3.1 Expected benefits

LDN is proposed to reduce or stop disease progression, reduce muscle spasm and fatigue, improve bladder control, mobility, pain[1].

3.2 Is there a plausible biological basis for effectiveness?

As an opiod antagonist LDN may result in an increased production of endorphins which could in theory reduce painful symptoms[1]. Doses used (3-4.5mg) are much lower than the licensed dose of 50mg. This theory has yet to be established by randomised controlled trials and would not reduce or stop disease progression.

3.3 Side-effects/complications

Reports are that side-effects are rare with LDN[1,9,10]. At the licensed dose for detoxification, side-effects include nausea, vomiting, abdominal pain, diarrhoea, constipation, reduced appetite, anxiety, sleep disturbance, headache, reduced energy, irritability[8] etc

3.4 Review of evidence (See Appendix 1. for Search Strategy and Summary of Results)

Chee et al examined the efficacy and quality of life in MS patients taking LDN 4.5mg per day[9]. This was a single centre double blind placebo-controlled crossover study evaluating the efficacy of 8 weeks of treatment with LDN as well as the quality of life as measured by the MS Quality of Life Index (MSQLI). The MSQLI is a quality of life assessment tool with 11 rating scales which asks the individual to report on mental and physical aspects of their condition including mental health, pain, perceived cognitive deficits, fatigue, visual, bladder and bowel symptoms and sexual satisfaction. This study was supported entirely by private contributions from patients. Patients were treated with LDN or placebo for 8 weeks followed by a 1 week washout period followed by 8 weeks of alternate study drug. Subjects being treated with DMTs were eligible to participate unless they had started a DMT within 3 months of study entry. Not all subjects enrolled in this study were on DMTs. Patient numbers were low (n=80) with completed data for only 60 patients due to a high dropout rate and administrative errors, substantially reducing the trial's statistical power.

MSQLI was measured at baseline then following each 8 week period of study drug. The investigators found that LDN improved the mental health outcome measures of MSQLI specifically the mental component summary (MCS), the mental health inventory (MHI) and perceived deficits questionnaire (PDQ). Improvements were also

seen in the pain effects scale (PES). Order of treatment with LDN or placebo did not influence the outcome however when the10 subjects who dropped out of the trial were included, statistical significance was only retained for MHI. No improvement was seen in physical quality of life (such as fatigue, bowel and bladder control, sexual satisfaction, and visual function). This trial did not measure EDSS. The duration of this study was short at only 8 weeks and there were no objective measurements of data as all data recorded was self-reported.

The main adverse effect, vivid dreaming was reported in both the placebo and active groups during the first week of treatment.

The investigators emphasized that the results did not support the use of LDN over proven MS treatments and that further studies with LDN in MS are warranted.

Another study involving LDN use in MS involved 40 adult Italian patients with a definite diagnosis of primary progressive MS[10]. This was an open, uncontrolled, 6 month study to assess safety and tolerability of LDN. Efficacy was assessed as a secondary outcome. Patients had to have suffered from 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 being treated with opiods were excluded. The starting dose was of 2mg, increased up 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 begining of LDN treatment and 1 month after the end of the study. The follow up visits assessed disease progression and adverse effects. Thirty five patients completed the study. One patient stopped due to disease progression, 3 patients stopped due to adverse effects and 1 patients stopped because they took an opioid based analgesic.

The majority of effects (95%) were classified as minor and 27 patients experienced at least 1 adverse effect. One third of adverse events were haematological abnormalities – increases in gamma-glutamyl-transpeptidase, bilirubin, liver enzymes and cholesterol levels were noted and some patients had leucopenia.

This study found spasticity was significantly improved in 47.4% of patients, remaining stable in 42.1%. 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. No statistically significant improvement in quality of life was noted.

The authors conclude that the data indicate 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 LDN.

4. Summary of Key Points for Consideration

4.1 Priority

LDN is currently prescribed in GP practices within Surrey at a cost of approximately £23,135 per annum. This is limited evidence of efficacy to support treatment with LDN and this money would be better invested on more effective treatments or procedures.

4.2 National guidance:
The Medicines and Healthcare products Regulatory Agency (MHRA) have not approved LDN for MS.

The Multiple Sclerosis Society does not support LDN for MS and states:
Currently there is not enough evidence-based information to prove LDN is an effective treatment for MS. The results of the most recent clinical trials are an important step in determining if there is any benefit for people with MS and the MS Society welcomes this research.LDN is not licensed for the treatment of MS in the UK. Some people with MS in the UK may have been prescribed LDN by their own GPs; however many GP's are reluctant to prescribe LDN in the absence of phase III clinical trial evidence that the drug is clinically beneficial.The MS Society supports an evidence-based approach to research and as such does not recommend that people take unproven treatments outside of a properly regulated clinical trial[13].

4.3 Efficacy
A small randomised placebo controlled pilot study of 80 patients found improvements in the mental health inventory aspect of MSQLI. Duration of treatment was only 8 weeks and patients' self-reported data. Another smaller open label uncontrolled pilot study of 40 Italian patients found significant improvements in spasticity. This study also found there was a statistically significant increase in pain and no improvement in quality of life was noted.

4.4 Potential Benefits over existing therapy: This has yet to be demonstrated.

4.5 Potential disadvantages: There are a number of disadvantages which include
a) Limited evidence to support effectiveness therefore not a cost effective use of scarce NHS resources
b) Potential to interact with licensed MS treatments.
c) Unlicensed for this indication
d) Supply: LDN is a specials product and is expensive (wholesaler ordering)
e) Side effects of treatment with LDN.

4.6 Budgetary Impact

4.6.1 Cost: LDN is classed as a "specials" product. These are expensive due to wholesaler ordering and costs vary significantly depending on the wholesaler used. At this present time, NHS Surrey has no control over how specials are ordered. The wholesaler IDIS charges £319.20 ex VAT for 30 x 3mg capsules and £364.80 ex VAT for 60 x 4.5mg capsules[11]. Added to this are out of pocket expenses charged by the pharmacist filling the prescription (2% of drug costs which are applicable on all drugs over a £100[12)].

The Multiple Sclerosis Resource Centre advises patients that supplies can be ordered from Dickson's Pharmacy in Glasgow. The liquid suspension costs £15 for a month's prescription and the capsules (3mg or 4.5mg) costs £30 for 30[1]. Very few pharmacies would order directly from Dickson's pharmacy as the majority order via a wholesaler.

4.6.2 Precedent setting: In the last year NHS Surrey spend £23,135 on LDN. Spend per ASTRO was £3.33 compared with a National spend per ASTRO of £0.94.

5. Conclusions and Recommendations

Currently there is insufficient evidence to support the prescribing of LDN in MS and further well designed randomised controlled trials are required. A small pilot uncontrolled, open study has indicated that LDN is a relatively safe, well tolerated drug and can improve spasticity. A small randomised placebo controlled trial of short duration with a high drop out rate and high administrative error showed the only significant improvement as reported by patients was a measure of mental health, the mental health inventory (1 out of 11 rating scales on MSQLI).

LDN should be regarded as an experimental treatment with no guaranteed benefits with the potential to interact with prescribed licensed treatments for MS.

Recommendation:
NHS Surrey does not support the prescribing of LDN for the treatment of MS due to limited evidence to support safety and efficacy.

Clinicians with patients currently prescribed LDN are urged to review their patients.

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Appendix 1: Evidence search

Search terms used: Naltrexone, low dose naltrexone, multiple sclerosis,

Resource	Used in this review?
National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.	✓
National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/ NICE produces national guidance in three areas of health: 1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.	✓ (through NHL)
Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.	✓(through NHL)
Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/	✓(through NHL)

CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database	
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/ Scottish equivalent of NICE	✓
Medical Services Advisory Committee (Australia) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1 The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.	✓
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.	✓

Evidence retrieved

Guidelines
Nil

Reviews:
UK Medicines Information (UKMI) Medicines Q & As October 2009
Reviews the evidence for LDN in MS and highlights that it is difficult to satisfactorily comment on the efficacy and safety of a product when clinical trials are lacking. Ancedotal evidence is unreliable when assessing the safety and efficacy of any medicine. Information presented on websites is not subject to peer review and must be interpreted cautiously.

Journals

Study	Design	No	Results

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Title: Pilot trial of low dose naltrexone and quality of life in MS **Citation:** Annals of Neurology Published Online: 19 Feb 2010 **Author(s):** Bruce A.C. Cree *, Elena Kornyeyeva, Douglas S. Goodin	Double blind randomised placebo-controlled cross over study comparing 4.5mg naltrexone	80	80 subjects with clinically definite multiple sclerosis were enrolled and 60 subjects completed the trial. 10 withdrew before completing the first trial period: 8 for personal reasons, 1 for a non-MS related adverse event and 1 for perceived benefit. Database management errors occurred in 4 other subjects and quality of life surveys were incomplete in 6 subjects for unknown reasons. The high rate of subject dropout and data management errors substantially reduced the trial's statistical power. LDN was well tolerated and serious adverse events did not occur. LDN was associated with significant improvement on the following mental health quality of life measures: a 3.3 point improvement on the Mental Component Summary score of the SF-36 (P=.04), a 6 point improvement on the Mental Health Inventory (P<.01), a 1.6 point improvement on the Pain Effects Scale (P=.04) and a 2.4 point improvement on the Perceived Deficits Questionnaire (P=.05). Including the 10 patients who dropped out meant that only MHI was significant. Further studies with LDN in MS are warranted.
Title: A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis **Citation:** Multiple Sclerosis, 2008, vol./is. 14/8(1076-1083), 1352-4585 (2008) **Author(s):** Gironi M.,Martinelli-Boneschi F.,Sacerdote P et al	Open uncontrolled 6 month study	40	The primary end points were safety and tolerability. Secondary outcomes were efficacy on spasticity, pain, fatigue, depression, and quality of life. Clinical and biochemical evaluations were serially performed. Protein concentration of beta-endorphins (BE) and mRNA levels and allelic variants of the mu-opiod receptor gene (OPRM1) were analyzed. Five dropouts and two major adverse events occurred. The remaining adverse events did not interfere with daily living. Neurological disability progressed in only one patient. A significant reduction of spasticity was measured at the end of the trial. BE concentration increased during the trial, but no association was found between OPRM1 variants and improvement of spasticity.

Appendix 2: Grading of evidence

- Ia: systematic review or meta-analysis of randomised controlled trials
- Ib: at least one randomised controlled trial
- IIa: at least one well-designed controlled study without randomisation
- IIb: at least one well-designed quasi-experimental study, such as a cohort study

- III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
- IV: expert committee reports, opinions and/or clinical experience of respected authorities

Appendix 3: References

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