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The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: a randomized placebo-controlled trial

Naser Sharafaddinzadeh¹, Ali Moghtaderi²,
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Abstract

Background: Low-dose naltrexone (LDN) may promote psychological well-being as well as generalized health especially in autoimmune disorders. The objective of this study is to assess the effect of LDN on the Quality of Life (QoL) of patients with relapsing–remitting and secondary progressive multiple sclerosis (MS) using the scales and composite scores of the MSQoL-54 questionnaire.

Methods: A 17-week randomized, double-blind, placebo-controlled, parallel-group, crossover-design clinical trial was conducted in two universities. A total of 96 adult patients aged between 15 and 65 years with relapsing–remitting (RR) or secondary progressive (SP) clinically definite MS with disease duration longer than 6 months enrolled into the study. The primary outcome of the study was comparison of the scores of physical and mental health by conducting independent *t*-test of the results obtained in the middle and at the end of study between the two groups.

Results: 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 QoL did not show any meaningful statistically 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.

Conclusion: 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.

Keywords

efficacy, low-dose naltrexone, multiple sclerosis, MSQoL-54

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Introduction

Naltrexone is a long-lasting opiate receptor antagonist. It is an orally effective agent and has been approved by the FDA for treating opiate addiction since 1984. Its main effect is blockade of the pleasure promoting μ and δ opioid receptors.^{1,2} It has less antagonism with κ opioid receptors³ and substantial effect on recently discovered orphanin FQ opioid family receptors.¹

A number of clinical studies suggest that the endogenous opioids may be involved in multiple sclerosis (MS). It was demonstrated that there is an increase in the level of β -endorphin in the peripheral blood mononuclear cells (PBMC) of MS patients in the relapse phase. Low-dose naltrexone (LDN) may block opioid receptors intermittently. The body response will be an increase in the production of opioid peptides and

receptors.⁴ It may promote psychological well-being as well as generalized health especially in autoimmune disorders. Temporary blockade of opioid receptors may induce upregulation of mood enhancing endorphins and probably will augment dopamine activity.

All of the above-mentioned mechanisms may further promote positive mentality.¹ Recently, it was reported that in experimental auto-immune encephalomyelitis,

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LDN-treated mice without behavioural signs of disease had markedly lower levels of activated astrocytes and demyelination. These results may imply that endogenous opioids, evoked by LDN administration are inhibitory to the onset and progression of experimental autoimmune encephalomyelitis, and suggest that clinical trials using LDN are merited in MS.⁴ There are indirect evidences showing ultra-LDN and LDN facilitates the analgesic effect of opioids and maintenance of drug abstinence in former opiate addicts.^{5,6}

The normal daily dose of 50–100 mg naltrexone is extensively used for the treatment of chronic alcoholics and opioid abuse.⁷ In contrast, LDN is generally less than 4.5 mg/d and most adults will consume less than 0.08 mg/kg each day. In animal studies, it has been illustrated that LDN will temporarily block opioid receptors and may induce β -endorphins, μ , δ and κ opioid receptors after 6 hours. It may trigger prolonged release of β -endorphins and will induce morphine analgesia.^{8–10} The effects of β -endorphins are on hypothalamic neurons which are traditionally considered as the mood and pain control centre in the human body. Despite that it is not a disease-modifying drug, the released endocrine secretions may reduce inflammatory mediators in immune-related diseases such as fibromyalgia rheumatic¹¹, Crohn's disease¹², and MS.^{8,13}

In chronic diseases with physical impairment, well-being and the state of feeling healthy seems to be as important as increasing survival. Attempts to develop simple methods to measure Quality of Life (QoL) in MS due to obvious neurological impairments has particular value especially after introducing disease-modifying drugs in recent decades. Health-related QoL questionnaires have become popular for measuring patient-assessed health status. MS Quality of Life-54 (MSQoL-54) is a useful multidimensional construct that includes physical, mental, and social health factors. It is increasingly recognized as a measuring tool for assessing health policy surveys in MS patients.¹⁴

The objective of this particular study is to assess the effect of LDN on the QoL of patients with relapsing–remitting and secondary progressive MS using the scales and composite scores of the MSQoL-54 questionnaire.

Materials and methods

Patient selection

A randomized, double-blind, placebo-controlled, parallel-group, crossover-design clinical trial was carried out in two centres from March 2007 to September 2009. The study was approved by the research ethics committees of both universities. A total of 106 adult patients with relapsing–remitting (RR) or secondary progressive

(SP) clinically definite MS participated in the study based on McDonald criteria.^{15,16} Eighty patients were enrolled from the coordinating centre, Jondi-Shapoor University School of Medicine, Ahwaz, south-western Iran, and 26 patients from the second centre, Zahedan University School of Medicine, Zahedan, south-eastern Iran. During the trial, 10 patients from both centres were excluded from the study due to exacerbation of their symptoms or the tendency to not continue the survey. The inclusion criteria were patients with age between 15 and 65 years, disease duration longer than 6 months, not treated with disease-modifying drugs, and taking medication for at least 3 months without changing or discontinuing the medication during the 17 weeks of the study-period. They were instructed not to change or start disease-modifying or symptomatic therapies for MS during the trial. Women of child-bearing age were asked to use a barrier method of contraception during the trial to prevent pregnancy. A negative pregnancy test for women was mandatory when the trial started. Patients were excluded if they had a chronic opioid agonists use (i.e. any narcotic medication including hydroxycodon and codeine-containing preparations) or immunosuppressive drugs such as cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, natalizumab, rituximab, and alemtuzumab, or other immune-suppressants at the time of inclusion. Serotonergic and other antidepressant drugs were accepted if the dosage was not changed in the 3-month period preceding the trial and maintained during the trial.

Questionnaire

After informed consent was obtained for the study, all participants filled out a questionnaire. Scales and composite scores of recently validated Persian version of the MSQoL-54 inventory were used.¹⁷ The outcome of the study was comparison of the scores of physical and mental health, measured by composite scales of the MSQoL-54 questionnaire between the treated and placebo groups. Once included, using blocked randomization technique; patients were randomly assigned to one of the two groups in order to balance baseline confounding variables. The first group (group A) was assigned to start with LDN (4.5 mg capsule) for 8 weeks and then switched to placebo for another 8 weeks. The authors did just the opposite for the second group (group B). To prevent residual influence of the intervention on the outcome, the researchers introduced an untreated 1-week washout-period between the end of the active treatment and beginning of the control period (placebo treatment) and vice versa for the other group. Totally, the trial duration lasted 17 weeks. The drugs had to be used every night before

going to bed between 9:00 p.m. and 3:00 a.m. Neither the patients nor the physicians were aware of the patients' treatment group until the study was completed and the results were decoded. Patients were requested to continue their medications till the end of the trial. They were asked to answer a Persian version of the MSQoL-54 questionnaire at the beginning of the trial and in weeks 8 and 17. Physical examination and medical/neurological history were recorded during the first visit to determine patients' eligibility. Follow-up visits were scheduled for weeks 8 and 17 (end of the study). At each evaluation visit, the patients were assessed with regard to history and physical/neurological examination, Expanded Disability Status Scale (EDSS) measuring,^{18,19} and adverse events. Additional visits were performed at the time of an adverse event occurrence. Disease status was categorized as mild (0–2.5), moderate (3–5.5), and severe (6–10) using EDSS score.

Statistical analysis

The MSQoL-54 scores were linearly transformed into 0–100 scales; the higher the transformed score, the better the patient's health-related QoL. Using SPSS software for Windows, Version 11 (SPSS Inc., Chicago, IL, USA), median, arithmetic mean, and standard deviation values for different variables were calculated. Statistical analyses were performed for each group. After an evaluation of the assumption of normal distribution, an independent student *t*-test and chi-squared tests were applied to compare continuous (age, disease duration, and EDSS scores before starting the trial) and dichotomous variables (sex, MS type, marriage, and EDSS group) between two groups (A and B) respectively. In order to do inferential statistics, we conducted independent *t*-test of the results obtained at weeks 8 and 17, to compare the scales and composite scores of the MSQoL-54 during the active treatment and placebo cycles after comparison of the mean scores between treated and placebo groups, adjusting for differences in the baseline scores. Comparisons were labeled as statistically significant at the conventional *p*-value of less than 0.05.

Results

A total of 106 patients with RRMS or SPMS enrolled into the study but before finishing the first part of the study only 96 patients remained in the study. Ten cases were excluded from the study (Figure 1). Table 1 shows compared clinical and demographic characteristics of two patient groups at the beginning of the trial. Fifty patients completed the 17-week therapy in group A and 46 in group B. Four patients in each group dropped out during the study due to exacerbation of their symptoms

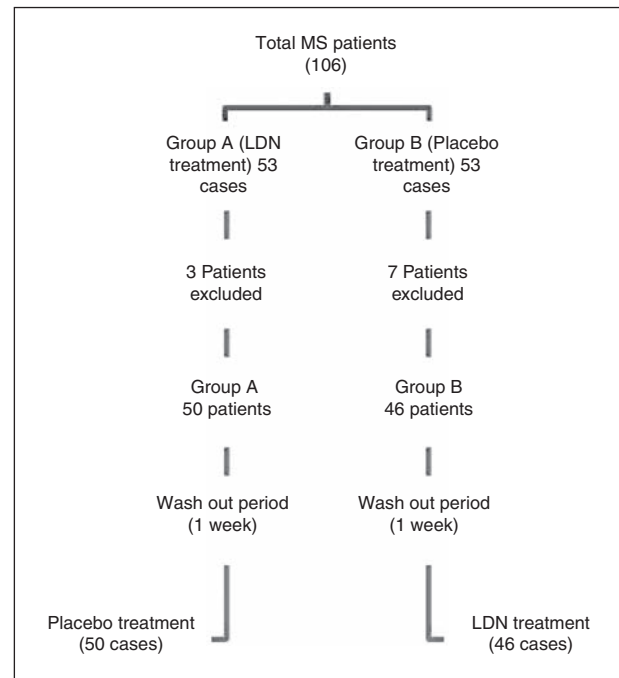


Figure 1. Trial profile.

during the first 2 weeks of trial and two patients due to tendency to not continue the study after the first 6 weeks. The compliance of the remaining patients was generally acceptable. The most common adverse events documented in our trial were minor and did not interfere with function (grade I) or daily living activities (grade II), tolerable and disappeared after the end of the treatment. Nausea, epigastric pain, mood alteration, mild irritability, headache, and joint pain were the main recorded adverse events. Such symptoms are transitory, do not interfere with function, and thus did not lead to any change in the dosage of the treatment. No major adverse events classified as grade III (severe) or grade IV (life threatening or disabling) were recorded. The data in Table 2 show mental and physical health composite scores of the patients before starting trial. Other 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 QoL did not show any statistically significant difference between both trial groups except for health perception. Statistical analysis did not reveal any change for all of the above-mentioned variables before starting the trial, in the middle, and at week 17 (Tables 3 and 4).

Discussion

According to Miltenburger, it is estimated that multiple sclerosis affected more than one million people all around the world.²⁰ EDSS is the most common

Table 1. Compared clinical and demographic characteristics of patients in two groups before starting trial

Patient characteristic	Total patients (n = 96)	Group A (n = 50)	Group B (n = 46)	p-value between group A and B
Female : male (% female)	73 : 23 (76%)	34 : 16 (68%)	39 : 7 (85%)	0.06
Age (years) (mean \pm SD)	34.81 \pm 9.31	35.5 \pm 8.71	34.07 \pm 9.96	0.14
Disease duration (years) (mean \pm SD)	5.95 \pm 4.48	6.79 \pm 3.9	5.05 \pm 4.93	0.72
MS type				
RRMS	71 (74%)	35 (70%)	36 (78%)	0.35
SPMS	25 (26%)	15 (30%)	10 (22%)	0.39
Married : single (% married)	65 : 31 (68%)	33 : 17 (66%)	32 : 14 (70%)	0.70
EDSS score (mean \pm SD)	3.18 \pm 1.87	3.34 \pm 1.87	3.00 \pm 1.86	0.92
EDSS group (%)				
Mild disability	50 (52%)	25 (50%)	25 (54%)	0.98
Moderate disability	30 (31%)	15 (30%)	15 (33%)	0.47
Severe disability	16 (17%)	10 (20%)	6 (13%)	0.70

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RR, relapsing–remitting; SP, secondary progressive.

Table 2. Comparing characteristics of patients in two groups before starting trial

Variable	Total patients (n = 96)	Group A (n = 50)	Group B (n = 46)	p-value between group A and B
Mental health composite score (mean \pm SD)	56.06 \pm 19.18	55.24 \pm 19.22	56.94 \pm 19.30	0.988
Physical health composite score (mean \pm SD)	52.16 \pm 18.21	48.92 \pm 16.20	55.67 \pm 19.74	0.073
Health perception (mean \pm SD)	49.01 \pm 18.84	46.90 \pm 15.18	51.30 \pm 22.09	0.006

Table 3. Comparing characteristics of patients in two groups at week 8

Variable	Total patients (n = 96)	Group A (n = 50)	Group B (n = 46)	p-value between group A and B
Mental health composite score (mean \pm SD)	58.04 \pm 20.27	56.20 \pm 21.45	60.03 \pm 18.93	0.783
Physical health composite score (mean \pm SD)	55.05 \pm 18.98	53.59 \pm 17.17	56.64 \pm 20.84	0.208
Health perception (mean \pm SD)	51.46 \pm 20.00	46.20 \pm 14.16	57.17 \pm 23.70	0.006

Table 4. Comparing characteristics of patients in two groups at week 17

Variable	Total patients (n = 96)	Group A (n = 50)	Group B (n = 46)	p-value between group A and B
Mental health composite score (mean \pm SD)	60.01 \pm 19.01	61.65 \pm 19.21	58.23 \pm 18.83	0.238
Physical health composite score (mean \pm SD)	55.80 \pm 18.50	53.19 \pm 16.28	58.64 \pm 20.43	0.126
Health perception (mean \pm SD)	52.14 \pm 17.86	47.60 \pm 15.33	57.07 \pm 19.22	0.007

measure of disability and the primary focus of the scale is on the physical impairment. It clearly illustrates the fact that EDSS weights mobility more than the other aspects of health.²¹ Additionally, QoL is one of the main features of health-related issues in patients with chronic conditions such as multiple sclerosis. The

psychosocial consequences have recently become the focus of research.²² Health-related QoL instruments are expected to be of particular value to assess the treatment results, both for the physicians and for the patients. It plays a major role in recognizing the disease features and helps clinicians, caregivers, and

health-care providers to point priorities of the patients' expectations and ambitions and match them to the treatment goals. Concerning the fact that more than 100 papers have been published about the QoL in MS since 1991, many clinicians mistrust such types of research and the questionnaires are used little in the routine clinical practice for MS patients.²³

There are some reports supporting the use of LDN for reducing MS relapses by the lay public, especially in UK. Patient self-assessed surveys attempt to assess the average rate of relapses and they lend support to the view that the attacks were decreased to 0.2 per year.²⁴ It was theorized that LDN may enhance the QoL through increasing both rewards and energy function from links between μ opioid receptors and central dopamine neurons in the mesencephalon.¹ To the best of the authors' knowledge, this is the first therapeutic trial aimed at assessing the QoL in patients with relapsing–remitting and secondary progressive MS consuming LDN. Although adverse effects of LDN is minimal and all of them are categorized in minor groups but the QoL has not been changed based on the MSQoL-54 questionnaire. Of course, many patients in this trial reported beneficial effects on bladder function (decrease in frequency or incontinence) but it was not confirmed by statistical analyses.

Gironi et al.⁸ recently published an open label trial on primary progressive MS cases without a control group. LDN efficacy on pain, fatigue, depression, and spasticity were assessed because of the frequency of those symptoms in MS patients. Based on the study it was suggested that the only beneficial effect of the LDN was on spasticity. As it was reported, the QoL had improved in many cases but there were not any statistical supporting evidence at the end of the study. Increased intracellular concentration of β -endorphin in the PBMCs of the study group was the only important finding.

The real biological mechanism of LDN is not known but theoretically LDN may increase β -endorphins by triggering PBMC.⁸ β -endorphin is an opioid peptide with known effects on modulation of pain, endocrine secretion, and recently for its immunomodulating effects. The main sources are the arcuate nucleus of the hypothalamus and the intermediate pituitary gland.²⁵ Different studies also confirmed that cannabinoids administration in MS patients will improve bodily pain and mental health by inducing β -endorphin release.^{26,27}

As it was earlier stated, factor analysis revealed that health perception scores are statistically different in both groups before starting, in the middle, and at the end of the study. Other variables were not shown to be different in two groups. Health perception is based on five questions as a component of physical health

composite in MSQoL-54 questionnaire. General questions are asked in the QoL and it probably depends largely on the patient's views about life. There is a general consensus that many psychosocial, religious, and physical factors are effective in answering those kinds of multidimensional health-related questions thus the assessment is always subjective.²⁰ Religious beliefs of the patients especially in eastern countries are important factors to tolerate the long life problems of chronic diseases such as MS and its complications. Many patients with chronic diseases such as cancer and MS often depend on their trust in a higher power; their religious beliefs help them to cope with their illness.^{28,29} Other factors of the physical health composite depend on the physical capabilities of the patients. Regarding health perception, the difference between two groups may be related to their social and religious beliefs. However the important issue is whether the difference is clinically as well as statistically meaningful or not.

In conclusion, this study clearly indicates that LDN is a relatively safe therapeutic option in RRMS and SPMS patients but the trial duration is not long enough. Potentially LDN may modulate both opioid and immune systems and expand the field for clinical experimentation in the regulation of immune-mediated diseases such as MS. Finally, we draw the conclusion that its efficacy is under question and probably a long duration trial or administering ultra-LDN may be needed in the future to better understand what patients would feel and what they would need.

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Conflict of interest

Al-Havi[®] provided naltrexone powder for the study. This company had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

References

1. Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life. *Med Hypotheses* 2009; 72: 333–337.
2. Weerts EM, Kim YK, Wand GS, et al. Differences in delta- and mu-opioid receptor blockade measured by positron emission tomography in naltrexone-treated recently abstinent alcohol-dependent subjects. *Neuropsychopharmacology* 2008; 33: 653–665.

3. Gharagozlou P, Hashemi E, DeLorey TM, Clark JD, Lameh J. Pharmacological profiles of opioid ligands at kappa opioid receptors. *BMC Pharmacol* 2006; 6: 3.
4. Zagon IS, Rahn KA, Turel AP, McLaughlin PJ. Endogenous opioids regulate expression of experimental autoimmune encephalomyelitis: a new paradigm for the treatment of multiple sclerosis. *Exp Biol Med (Maywood)* 2009; 234: 1383–1392.
5. Mannelli P, Patkar AA, Peindl K, Murray HW, Wu LT, Hubbard R. Effectiveness of low-dose naltrexone in the post-detoxification treatment of opioid dependence. *J Clin Psychopharmacol* 2007; 27: 468–474.
6. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *J Pain* 2006; 7: 937–946.
7. Crabtree BL. Review of naltrexone, a long-acting opiate antagonist. *Clin Pharm* 1984; 3: 273–280.
8. Gironi M, Martinelli-Boneschi F, Sacerdote P, et al. A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. *Mult Scler* 2008; 14: 1076–1083.
9. Rajashekara V, Patel CN, Patel K, Purohit V, Yoburn BC. Chronic opioid antagonist treatment dose-dependently regulates mu-opioid receptors and trafficking proteins in vivo. *Pharmacol Biochem Behav* 2003; 75: 909–913.
10. Yoburn BC, Goodman RR, Cohen AH, Pasternak GW, Inturrisi CE. Increased analgesic potency of morphine and increased brain opioid binding sites in the rat following chronic naltrexone treatment. *Life Sci* 1985; 36: 2325–2332.
11. Panerai AE, Vecchiet J, Panzeri P, et al. Peripheral blood mononuclear cell beta-endorphin concentration is decreased in chronic fatigue syndrome and fibromyalgia but not in depression: preliminary report. *Clin J Pain* 2002; 18: 270–273.
12. Wiedermann CJ, Sacerdote P, Propst A, et al. Decreased beta-endorphin content in peripheral blood mononuclear leukocytes from patients with Crohn's disease. *Brain Behav Immun* 1994; 8: 261–269.
13. Gironi M, Furlan R, Rovaris M, et al. Beta endorphin concentrations in PBMC of patients with different clinical phenotypes of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2003; 74: 495–497.
14. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Qual Life Res* 1995; 4: 187–206.
15. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; 50: 121–127.
16. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald Criteria'. *Ann Neurol* 2005; 58: 840–846.
17. Ghaem H, Haghghi AB, Jafari P, Nikseresht AR. Validity and reliability of the Persian version of the multiple sclerosis quality of life questionnaire. *Neurol India* 2007; 55: 369–375.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983; 33: 1444–1452.
19. Kurtzke JF. Disability rating scales in multiple sclerosis. *Ann N Y Acad Sci* 1984; 436: 347–360.
20. Miltenburger C, Kobelt G. Quality of life and cost of multiple sclerosis. *Clin Neurol Neurosurg* 2002; 104: 272–275.
21. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. *Neurology* 1999; 53: 1098–1103.
22. Aronson KJ. Quality of life among persons with multiple sclerosis and their caregivers. *Neurology* 1997; 48: 74–80.
23. Rothwell PM. Quality of life in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998; 65: 433.
24. Agrawal YP. Low dose naltrexone therapy in multiple sclerosis. *Med Hypoth* 2005; 64: 721–724.
25. Gironi M, Martinelli V, Brambilla E, et al. Beta-endorphin concentrations in peripheral blood mononuclear cells of patients with multiple sclerosis: effects of treatment with interferon beta. *Arch Neurol* 2000; 57: 1178–1181.
26. Baker D, Pryce G, Croxford JL, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 2000; 404: 84–87.
27. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; 362: 1517–1526.
28. Benjamins MR, Finlayson M. Using religious services to improve health: findings from a sample of middle-aged and older adults with multiple sclerosis. *J Aging Health* 2007; 19: 537–553.
29. Büssing A, Ostermann T, Koenig HG. Relevance of religion and spirituality in German patients with chronic diseases. *Int J Psychiatry Med* 2007; 37: 39–57.