Pilot Trial of Low-Dose Naltrexone and Quality of Life in Multiple Sclerosis

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Objective: To evaluate the efficacy of 4.5mg nightly naltrexone on the quality of life of multiple sclerosis (MS) patients.
Methods: This single-center, double-masked, placebo-controlled, crossover study evaluated the efficacy of 8 weeks of treatment with 4.5mg nightly naltrexone (low-dose naltrexone, LDN) on self-reported quality of life of MS patients.
Results: Eighty subjects with clinically definite MS were enrolled, and 60 subjects completed the trial. Ten 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 Short Form-36 General Health Survey ($p = 0.04$), a 6-point improvement on the Mental Health Inventory ($p < 0.01$), a 1.6-point improvement on the Pain Effects Scale ($p = .04$), and a 2.4-point improvement on the Perceived Deficits Questionnaire ($p = 0.05$).
Interpretation: LDN significantly improved mental health quality of life indices. Further studies with LDN in MS are warranted.

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Naltrexone is a mu opiate receptor antagonist approved by the US Food and Drug Administration (FDA) for treatment of opiate addiction. Low-dose naltrexone (LDN) was found to enhance the pain-relieving effects of opiate agonists[1,2] and also to be beneficial in opioid detoxification.[3] LDN is proposed to normalize endogenous endorphin levels; this effect on endorphins might be beneficial in autoimmune disease. A small (N = 17) open label study in Crohn disease found that LDN improved active disease as measured by the Crohn disease activity index.[4] An open label study in 40 primary progressive multiple sclerosis (MS) patients found that spasticity was significantly reduced after 6 months of treatment with LDN compared to baseline.[5] This study also found that LDN treatment increased lymphocyte intracellular B-endorphin concentrations over baseline values. MS patients who use off-label LDN anecdotally report that LDN improves their overall quality of life (QOL) and have wanted to have this proposition evaluated systematically. Based on interviews with 5 North American pharmacies known to compound LDN, we estimate that several thousand MS patients currently use LDN. Here we report the results of a patient-sponsored, randomized, placebo-controlled, crossover clinical trial that evaluated the impact of LDN on MS patient-reported outcomes as measured by the Multiple Sclerosis Quality of Life Inventory (MSQLI).[6]

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The patient sponsors of this study did not participate in the design, conduct, or analysis of the trial and did not help write the manuscript. To our knowledge, this is the first patient funded clinical trial in MS.

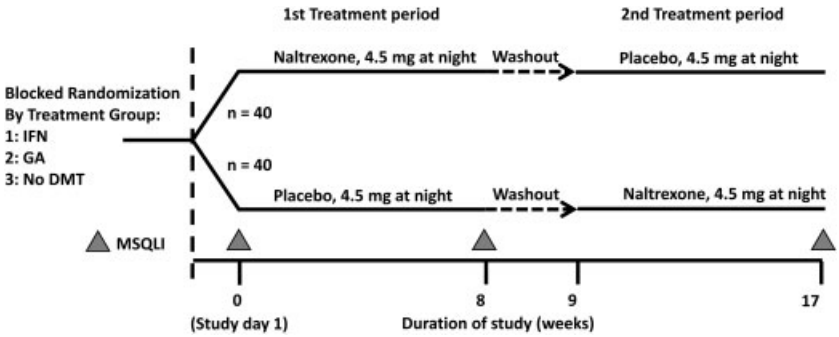

FIGURE 1: Study design. IFN = interferon; GA = glatiramer acetate; DMT = disease-modifying therapy; MSQLI = Multiple Sclerosis Quality of Life Inventory.

Patients and Methods

Study Design and Objectives

The current trial is a single-center, randomized, double-masked, placebo-controlled, crossover study that evaluated whether 8 weeks of treatment with nightly 4.5mg naltrexone improved the QOL of MS patients as measured by the MSQLI (Fig 1). Baseline demographics are shown in Table 1. This study was supported entirely by private contributions from MS patients and is the first patient-funded controlled clinical study in MS. 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. Thus, 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 crossover design was selected because it was hypothesized that 8 weeks of treatment with LDN might provide a short-term symptomatic benefit. A 1-week washout was selected because of the half-life of naltrexone is 4 hours, and that of its active metabolite, 6-β-naltrexol, is 13 hours (package insert). Thus the serum level would be effectively zero after a 1-week washout. Furthermore, because the MSQLI asks subjects to report on their symptoms during the last 4 weeks, the shortest period of time that subjects would have been off of LDN if they had they received LDN during the first study period was 5 weeks. Patients completed the MSQLI at baseline and after each study period. The study was approved by the University of California, San Francisco (UCSF) committee on human research.

Participation Criteria

Eighty patients between the ages of 18 and 75 with clinically definite multiple sclerosis (International Panel criteria) were enrolled utilizing the following inclusion/exclusion criteria. Subjects had to be willing to not change or start disease-modifying or symptomatic therapies for the duration of the trial. Subjects 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. Women of childbearing potential had to be willing to use a barrier method of contraception during the trial. Potential subjects were excluded from the study if they had started a disease-modifying therapy within 3 months of entry, had received treatment with chronic opiate agonists, were treated concurrently with both IFN and with GA, took immunosuppressive medications including natalizumab, were pregnant, were unable to read a computer screen and use a mouse, or were currently taking LDN.

Study Drug

Placebo and naltrexone capsules were compounded by the UCSF investigational pharmacy. Treatment codes were maintained by the investigational pharmacy. Concomitant medications and pill counts were assessed at each study visit. The MSQLI was administered using a Web-based system developed by QuesGen Systems (Burlingame, CA).

Outcome Measures

The MSQLI was administered at baseline, and then following each 8-week period of study drug administration (see Fig 1).

TABLE 1: Baseline Demographics

Mean age, yr	**49**
Women:men	36:24
Race	
White	54
Asian	2
Multiracial	2
Not specified	2
RRMS	31
SPMS	13
PPMS	15
PRMS	2
Concurrent IFN use	14
Concurrent GA use	14
No concurrent DMT	32

RRMS = relapsing/remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis; PRMS = progressive relapsing multiple sclerosis; IFN = interferon; GA = glatiramer acetate; DMT = disease-modifying therapy.

The MSQLI[6] is a QOL assessment tool developed for MS composed of 11 rating scales: the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the Short Form-36 General Health Survey (SF-36),[7,8] Mental Health Inventory (MHI), Pain Effects Scale (PES), Perceived Deficits Questionnaire (PDQ), Multiple Sclerosis Social Support Survey (MSSS), Modified Fatigue Impact Scale (MFIS), Impact of Visual Impairment Scale (IVIS), Bowel Control Scale (BWCS), Bladder Control Scale (BLCS), and the Sexual Satisfaction Scale (SSS). Subjects were required to complete the MSQLI within a 2-day window from completion of each study phase, that is, at 8 weeks $\pm$ 2 days. Subjects are asked to answer these surveys with regard to their relevant symptoms during the last 4 weeks. Adverse events and self-reported relapses, if any, were documented at each study visit. The Expanded Disability Status Scale[9] was not assessed following the 2 treatment periods. Improvement in QOL is characterized by an increase in the scores for the PCS, MCS, MHI, and MSSS and a decrease in scores for the MFIS, PES, PDQ, BWCS, BLCS, IVIS, and SSS.

Statistical Analysis

Because of the crossover design, the results were analyzed using a time series regression equation modeled for random effects and clustered by study subject. The prespecified analysis adjusted for sex, age, disease course (relapse remitting, secondary progressive, primary progressive, and relapsing progressive), current treatment (IFNβ, GA, or no disease-modifying therapy), race, baseline score, and study drug order.

Results

Eighty subjects were enrolled. Eight subjects voluntarily withdrew during the first treatment phase for personal reasons such as the inability to complete the MSQLI during the required window. One subject withdrew during the first study period because of perceived efficacy of LDN; at the end of the study, it was determined that this subject was initially treated with placebo. One withdrew secondary to ongoing symptoms from an unrelated preexisting medical condition (an acoustic neuroma). There was no correlation between study drug and subject withdrawals. Seventy subjects completed both treatment periods; however, data from all 3 MSQLI assessments were available for only 60 subjects. Ten subjects were dropped from analysis because of database management errors in 4 subjects and 6 uncompleted surveys. That 6 subjects did not complete 6 surveys was not detected until after the trial was complete. The reason for these uncompleted surveys is not known. The MSQLI was administered using a Web-based system specifically developed for this trial, and methods to insure completeness of data entry were not implemented at the time the trial was conducted. Because 10 subjects dropped out of the trial, and data management errors occurred in another 10 subjects, the statistical power of the trial was substantially weakened. However, we do not believe that this loss of information caused type I errors, because 9 of the 10 subjects who dropped out did so for reasons unrelated to the study. Furthermore, the data management errors were random rather than systematic.

In the preplanned analysis that adjusted for baseline covariates as well as an unadjusted analysis, 8 weeks of treatment with LDN significantly improved mental health QOL indices measured by the MCS of the SF-36, the MHI, and the PES, and there was a favorable trend for the PDQ (Table 2; see Fig 1). Order of treatment with LDN or placebo did not influence the outcome. Indeed, the only baseline covariate that had a statistically significant impact on the model was the baseline score, although the relatively small sample size precluded detection of subtle influences. An impact on physical QOL indices, including the PCS of the SF-36, MFIS, BWCS, BLCS, SSS, and IVIS, was not observed. Concurrent treatment with IFNβ or GA did not influence these outcomes. Figure 1 also demonstrated a prominent placebo effect in this study. To emphasize the preliminary nature of this small single-center study, a sensitivity analysis was conducted in which the 10 subjects who dropped out of the trial were included, imputing their baseline scores for the MSQLI assessments following both study drug periods. This introduces 16.7% noise into the statistical analysis and causes the MCS of the SF-36, PES, and PDQ observations favoring LDN to no longer be statistically significant; however, statistical significance is retained for the MHI ($p = .043$).

MS relapses were not reported by any patient during the study. For the 60 subjects who completed the study, adherence to the treatment protocol as measured by self-reporting and pill counts was excellent. The average medication possession ratio was 95.7%. Serious adverse events were not reported. The only potentially treatment-related adverse event was vivid dreaming reported in 7 placebo and 10 LDN treatment periods. Other adverse events reported in each treatment period were: fatigue (2 placebo and 1 LDN), flu-like symptoms (1 placebo), insomnia (1 placebo), loss of appetite (1 LDN), and sinus infection (1 LDN). Euphoria was not reported by any patient.

Discussion

This is the first randomized, placebo-controlled study of LDN in MS and the first patient-funded clinical trial in MS. Eight weeks of treatment with LDN was associated with improvement in all of the self-reported mental health outcome measures but not of the physical outcome measures of the MSQLI. That mental health outcome measures improved during a relatively short course of

TABLE 2: MSQLI Results

Scale	Baseline	Subscale Range	Placebo	LDN	ΔLDN-Placebo	*p*
SF-36 PCS	34.98	13.6-61.9	36.85	36.95	0.10	0.88
SF-36 MCS	44.32	15.6-70.0	46.77	50.07	3.30	0.04
PF	44.40	0-100	45.90	47.82	1.92	0.18
RP	25.42	0-100	36.00	43.08	7.08	0.18
BP	63.34	0-100	66.70	68.83	2.13	0.42
GH	50.76	0-100	52.78	52.46	−0.32	0.85
VT	33.60	0-90	42.60	44.72	1.92	0.52
SF	57.80	12.5-100	69.90	69.69	−0.21	0.95
RE	53.67	0-100	55.37	69.81	14.44	0.03
MH	65.22	0-100	66.92	72.12	5.2	0.02
MFIS	38.6	0-84	31.41	30.28	−1.13	0.53
PES	16.1	6-30	14.17	12.60	−1.57	0.04
SSS	9.7	4-24	9.14	8.97	−0.17	0.76
BLCS	5.1	0-22	4.44	5.06	0.62	0.17
BWCS	3.3	0-26	3.02	3.29	0.27	0.79
IVIS	1.7	0-15	1.42	1.47	0.05	0.83
PDQ	27.6	0-80	25.20	22.78	−2.42	0.05
MHI	63.5	0-100	65.65	71.65	6.00	<0.01
MSSS	77.1	0-100	72.76	74.11	1.35	0.43

The range is for the subscales rather than the range reported for the subjects in the study at baseline. MSQLI = Multiple Sclerosis Quality of Life Inventory; SF-36 = Short Form-36 General Health Survey; PCS = Physical Component Summary; MCS = Mental Component Summary; PF = Physical Functioning; RF = Role-Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role-Emotional; MH = Mental Health; MFIS = Modified Fatigue Impact Scale; PES = Pain Effects Scale; SSS = Sexual Satisfaction Survey; BLCS = Bladder Control Scale; BWCS = Bowel Control Scale; IVIS = Impact of Visual Impairment Scale; PDQ = Perceived Deficits Questionnaire; MHI = Mental Health Inventory; MSSS = Multiple Sclerosis Social Support Survey.

treatment with LDN suggests that LDN has a symptomatic effect in MS. These observations are consistent with anecdotal patient reports suggesting that LDN makes patients feel better.[10] It is possible that LDN increases β-endorphin levels,[5] and that this may correlate with improvement in mental health QOL. That LDN did not have an impact on self-reported physical functioning is to be expected because of the short duration of treatment. Whether LDN has benefit beyond 8 weeks of treatment, and whether LDN might improve physical functioning with extended treatment, are questions unanswered by this study design.

Benefits with respect to physical functioning might be anticipated from disease-modifying therapies that reduce neurological disability. However, that some patients will continue to accumulate neurological impairment despite treatment may confound this prediction. Indeed, studies with IFNβ, an immunomodulatory drug known to reduce the risk of neurological disability in MS, have not shown a consistent improvement in MS QOL.[11–17]

One explanation that might account for these discrepancies has to do with the impact of treatment itself. In relapsing/remitting MS, IFNα-2a did not improve QOL after 6 months; however, adverse events were significantly correlated with several SF-36 subscales.[18] Thus, the side effects of treatment with IFN negatively impact MS QOL, thereby confounding the potential benefits of disease-modifying treatment.

To date, the only US FDA-approved treatment for MS that has shown a benefit on MS QOL is natalizumab.[19] In a 2-year randomized controlled trial (RCT), treatment with natalizumab resulted in a 2-point difference in the PCS score and a 2.5-point difference in the MCS score of the SF-36 relative to placebo. In a second

2-year RCT, treatment with natalizumab plus IFNβ-1a resulted in a 2-point difference in the PCS score and a 1-point difference in the MCS score relative to IFNβ-1a alone. Although a 5-point change on either the MCS or PCS of the SF-36 is proposed to be the clinically relevant magnitude of change, the correlation between 2-point changes on these scales with objective measures of clinical efficacy in these 2 natalizumab clinical trials suggests that smaller changes may be clinically important for MS patients.

The effect of LDN on the mental component summary score of the SF-36 compares favorably to that of natalizumab, suggesting that the magnitude of difference relative to placebo for this measure is clinically relevant (a 3.3-point increase at 8 weeks for LDN compared to a 1.0- to 2.5-point increase at 2 years for natalizumab). This benefit for LDN treatment was supported by significant improvements on the mental health inventory (6 points), the pain effects scale (1.6 points), and the perceived deficits questionnaire (2.4 points). Because disease-modifying treatments have not demonstrated an effect on these scales, the clinical relevance of these magnitudes of change is not known. Nevertheless, the proportion of improvement on these other scales is similar to that of the MCS score of the SF-36.

That LDN had benefit with regard to patient-reported mental health, pain, and cognitive function raises the possibility that patients became unmasked to treatment. However, this cannot explain the findings, because unmasking with respect to treatment arm would be expected to abrogate the benefits of placebo and therefore the placebo QOL measures would either be the same or worse than baseline. In fact, these measures were better than baseline in both groups (Figs 2 and 3). Moreover, exit interviews conducted in a sample of the cohort confirmed that subjects were not able to guess the order of treatment.

Regression modeling showed that neither IFN nor

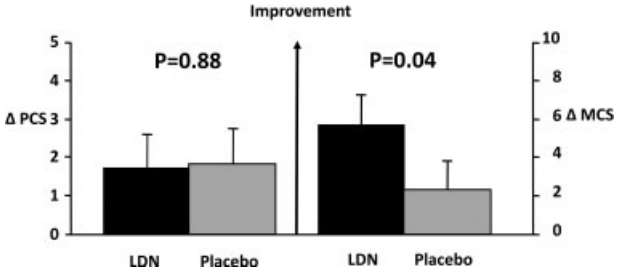

FIGURE 2: Short Form-36 General Health Survey Physical Component Summary (PCS) scale score (range, 13.6–61.9; baseline, 34.9) and Mental Component Summary (MCS) scale score (range, 15.6–70.0; baseline, 44.2). LDN = low-dose naltrexone.

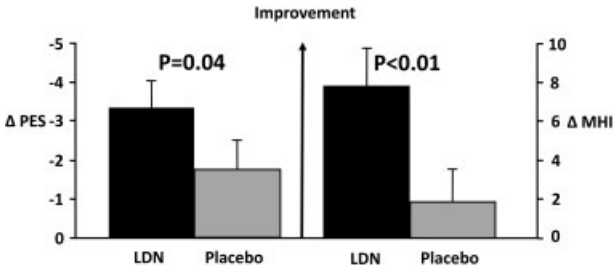

FIGURE 3: Pain Effects Scale (PES) (range, 6–30; baseline, 16.1) and Mental Health Inventory (MHI) (range, 0–100; baseline, 63.5). LDN = low-dose naltrexone.

GA treatment influenced QOL in this study. Because patients were required to be on treatment with these drugs for at least 3 months prior to enrollment, any effect of these drugs on QOL indices was likely preset at baseline and thus would not influence the study results. Furthermore, the lack of effect of IFN or GA on the outcomes suggests that there is not a negative interaction between these drugs and LDN. Interestingly, the only baseline variable that influenced the outcome measures was the baseline MSQLI scores. Subjects who experienced a poorer quality of life at baseline were more likely to benefit from treatment.

Despite the provocative observations that LDN may symptomatically improve some aspects of QOL in MS patients, it must be emphasized that the present study design did not assess LDN as a disease-modifying therapy. The results do not support use of LDN as an alternate to proven MS treatments such as IFNβ, GA, and natalizumab. Indeed, there is a misconception among some MS patients that LDN is incompatible with IFN usage, and the present study did not find evidence of such antagonism. In conclusion, in this exploratory, single-center study, 8 weeks of treatment with LDN was associated with symptomatic benefit with respect to mental health, pain, and perceived cognitive deficits in MS. Confirmation of these findings in a multicenter trial will be necessary to reach definite conclusions about the possible symptomatic benefit of LDN in MS. A longer duration of treatment is necessary to determine whether LDN has any benefit with respect to physical outcome measures. Immunological and endorphin studies may help elucidate the mechanism of action of LDN responsible for these observations.

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Potential Conflicts of Interest

Nothing to report.

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