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Low-dose naltrexone reduced anxiety in persons with multiple sclerosis during the COVID-19 pandemic

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ARTICLE INFO

Keywords:
Anxiety
Depression
Low dose naltrexone
Disease-modifying therapy
Multiple sclerosis

ABSTRACT

Persons with multiple sclerosis (PwMS) have been considered at high risk for vaccination and/or acquisition of COVID-19 related to their reduced immune systems and daily regimen of immune suppressing therapy. Substantiated and unsubstantiated reports on these unknown circumstances increased anxiety and depression. Low-dose naltrexone (LDN) is a potentially effective off-label therapy shown to be effective at controlling fatigue for several autoimmune disorders including MS. This study utilized a small population of PwMS from central Pennsylvania in order to determine whether LDN therapy altered their perceived anxiety or depression during the early months of COVID-19. Utilizing mailed surveys, self-reported anxiety and depression scores were found to be significantly lower for PwMS who were prescribed LDN either alone or as an adjuvant to a standard disease modifying therapy (DMT) in comparison to those on oral DMTs. The data suggest that the non-toxic, inexpensive biotherapeutic may be beneficial in lessening anxiety.

1. Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease associated with neurological impairment. The chronic reduced quality of life related to MS often leads to anxiety and depression. In 2020, the SARS-CoV-2 infectious disease led to the COVID-19 pandemic. The Center for Disease Control and Prevention announced early in the pandemic that individuals on immune-modulating drugs were at high risk for this disease or for contracting side-effects to vaccination, exacerbating anxiety and depression [1–4].

Not all persons with MS (PwMS) respond to standard disease modifying therapies (DMTs), and some are placed on the oral, off-label drug low-dose naltrexone (LDN) for fatigue or other issues [5,6]. The mechanism of action of LDN is based on the duration of opioid receptor blockade. Thus, the low doses of naltrexone (2.5–4 mg/day) block opioid receptors for a short period of time resulting in a biofeedback stimulus to increase circulating levels of β-endorphin and [Met5]-enkephalin [7]. One specific opioid receptor involved in this pathway is the Opioid Growth Factor Receptor (OGFr) that functions to mediate cellular homeostasis [7]. Clinical and pre-clinical studies have reported that these neuropeptides are often decreased in MS [7,8]. LDN is inexpensive, safe, and used effectively for treatment of fibromyalgia, Crohn’s disease, and MS [9]. Clinical studies have shown that long term treatment with LDN can contribute to stable disease and overall good health in PwMS [7–12], and may improve the balance of pro- and anti-inflammatory cytokines [11,12]. Because [Met5]-enkephalin inhibits cell proliferation and acts to dampen inflammatory cytokine proliferation, individuals with normal or high levels of this peptide report better overall perception of their physical and mental health [6–8,12].

During the COVID-19 pandemic, LDN usage escalated [5,6]. Our laboratory initially described the mechanism of LDN action and thus, we were interested in investigating the relationship of anxiety and depression in PwMS prescribed LDN. The hypothesis of this study is that PwMS taking LDN alone or in combination with DMTs have lower anxiety and/or depression scores than patients only prescribed oral DMTs.
2. Materials and methods

2.1. Data collection

The study design was approved (protocol #9784) by the Penn State College of Medicine Institutional Review Board, Human Subjects Protection Office. Data were collected as part of a larger project examining anxiety and depression in PwMS from March 2021 through July 2022. Completion of the survey was voluntary and considered informed consent. A survey packet including a cover letter explaining the project, a single page requesting demographic information (sex, age, treatment, length of disease) and information on COVID-19, the Hospital Anxiety and Depression Scale (HADS) [13] for anxiety (HADS-A) and depression (HADS-D), and a modification of the Beck Depression Inventory for multiple sclerosis (MS-BDI) surveys [14] were enclosed, along with a stamped, addressed envelope to return the information to the Penn State College of Medicine. Confirmed PwMS were mailed packets or given envelopes containing the surveys at the time of pre-determined clinical visits. There were no identifying codes assigning the surveys to specific individuals so follow-up was not possible.

2.2. Data analyses

Surveys were scored by multiple individuals, and data analyzed using GraphPad Prism 8.0 (GraphPad Software, San Diego). Non-parametric data (e.g., behavioral scores) were analyzed using Mann-Whitney tests, with Gaussian approximation. Parametric data (e.g., age, length of disease) were analyzed using two-tailed t-tests. Contingency chi-square tests were used to analyze the proportion of individuals with high (i.e., ≥ 8) behavioral scores. For all analyses, p values < 0.05 were considered significant.

3. Results

3.1. Demographics of the respondents

Over a 17-month period (March 2021 through July 2022), 150 surveys were collected. This report focused on individuals taking LDN alone or with another prescribed DMT (LDN + DMT group), and for comparison, were compared to a group of individuals taking oral medications (Oral DMT group). Forty-six completed surveys were included in the analysis establishing the LDN + DMT group (n = 14) and Oral DMT group (n = 32). Demographics of the PwMS are presented in Table 1. Two males and 10 females took LDN in combination with another DMT, and one male and one female took only LDN. The comparison group of 26 females and 5 males were prescribed oral DMTs including Tecfidera®/Vumerity® (n = 18), Aubagio® (n = 4), Gilenya® (n = 6), Mavenclad® (n = 2), and Dalfampridine® (n = 2). There were no differences in age between males and females within either group; ages ranged from 31 to 73 years.

The length of disease of these cohorts did not differ (Table 1). Individuals taking only LDN had a longer mean length of disease of 30 ± 14 years.

Table 1

| Disease, years | LDN + DMT (11-57) | Male (N) | LDN + DMT (11-57) | Male (N) | LDN + DMT (11-57) | Male (N) | LDN + DMT (11-57) | Male (N) |
|---------------|------------------|---------|------------------|---------|------------------|---------|------------------|---------|
| Female (range) | 60 ± 2.7 (11) | 64 ± 4.8 (3) | 20.4 ± 3.2 | 14.3 % | 60 ± 2.7 (11) | 64 ± 4.8 (3) | 20.4 ± 3.2 | 14.3 % |
| Male (range)   | 60 ± 2.7 (11) | 64 ± 4.8 (3) | 20.4 ± 3.2 | 14.3 % | 60 ± 2.7 (11) | 64 ± 4.8 (3) | 20.4 ± 3.2 | 14.3 % |

Data represent means ± S.E.M. No statistical differences were noted between groups using two-tailed t-tests.

Five individuals in the Oral DMT group and 2 females in the LDN + DMT groups indicated that they had tested positive for COVID-19, whereas no PwMS on LDN alone tested positive for COVID during the experimental time period.

3.2. Behavioral assessments

Anxiety and depression scores are presented in Table 2. The small sample size for the LDN + DMT group, and an even smaller cohort of males resulted in combining the data for males and females. HADS-A scores were significantly lower for those in the LDN + DMT group in comparison to the HADS-A scores for the Oral DMT group (p = 0.02). Two-sided chi-square analysis revealed a significant difference (p = 0.016) for the proportion of persons in the LDN + DMT group that scored ≥ 8 in comparison to the Oral DMT group, suggesting that the addition of LDN reduced anxiety. With regard to the HADS-D survey, the LDN + DMT group had scores of 3.3 on the HADS-D survey in comparison to the mean score of 5.2 for the Oral DMT group (p < 0.05). Only 2 individuals receiving LDN had scores > 8 for the HADS-D assessment in comparison to 7 individuals in the Oral DMT group. The MS-BDI survey also indicated significant differences between the Oral DMT and LDN + DMT groups (p = 0.03). Only one subject in the LDN + DMT group had a “positive” score of 12 in comparison to 7 people in the Oral DMT group with positive scores ranging from 8 to 12 (mean 9.7 ± 0.64); two-sided chi-square analysis revealed that these differences were significant at p = 0.013.

Individuals on LDN only had HADS-A scores of 3 or 4, HADS-D scores of 1 or 2, and MS-BDI scores of 0 or 2.

4. Discussion

This study demonstrated that in a small population of central Pennsylvania residents LDN alone or in combination with other oral DMTs reduced anxiety and depression such that these individuals had lower HADS-A scores than individuals only on oral DMTs. The MS International Federation published information on risk of COVID infection based on DMT use and assigned oral drugs as “low risk for infection” suggesting that most oral drugs were characterized as leading to significant suppression of immune response and therefore could be continued without concern [1-3]. Reder et al. [4] reported that comorbidities, obesity, and ancestry increased the risk of COVID-19 infection more than continuation with therapy. However, anti-CD20 therapies such as Ocrelizumab and Rituximab, have both good and bad effects on the immune system. These drugs reduce pro-inflammatory B cell proliferation and antibody production which is positive in terms of limiting myelin destruction, but they also result in lower immunity responses to offset COVID infection. A number of studies in Ireland [6] and elsewhere [5] concluded that LDN was safe and reduced symptomatology of COVID-19. The mechanism of action was postulated to involve positive immune-modulation. LDN therapy is prescribed off-label but is frequently used alone or in combination for treatment of fatigue, perhaps as a result of upregulation of neuropeptides including β-endorphin and [Met²]-enkephalin [8,9]. In this report, the study population is too small to determine specific medical responses, but in previous studies in our laboratory it was found that patients treated for

Table 2

| Group | HADS-A | HADS-D | BDI-MS |
|-------|--------|--------|--------|
| Oral DMT (n = 37) | 7.2 ± 0.71 | 5.2 ± 0.56 | 4.7 ± 0.63 |
| LDN + DMT (n = 14) | 4.3 ± 0.81 ** | 3.3 ± 0.89 * | 2.5 ± 0.88 * |

Data are means ± S.E.M. Data were analyzed using Kruskal-Wallis tests for non-parametric data; p < 0.05* and p < 0.02 (**).
up to 50 months with LDN had no significant differences in time 25-foot walking tests, clinical laboratory values, or changes in magnetic resonance imaging from individuals prescribed Copaxone® [8]. These data corroborate evidence that LDN has no harmful effects on PwMS [6,7,11,12] and may in fact reduce anxiety. Collectively, evidence supports well-designed clinical trials for the use of LDN as a first-line therapy.

Declaration of Conflict of Interests
PJM, LBO, SO, GAT, and ISZ declare no potential conflicts with respect to the research, authorship and/or publication. PAA declares the following potential conflicts: Consultant for Roche Pharmaceuticals, Consultant for Biogen, and Speakers’ Bureau for EMD Serono.

Data availability
Data will be available upon written request to the authors.

CRediT authorship contribution statement
Patricia J. McLaughlin: Conceptualization, Project administration, Writing – review & editing. Laura B. Odom: Data curation, Writing – review & editing. Peter A. Arnett: Supervision, Writing – review & editing. Shannon Orehek: Data curation, Writing – review & editing. Gary A. Thomas: Writing – review & editing. Ian S. Zagon: Conceptualization, Data curation, Writing – review & editing.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability
The data that has been used is confidential.

Acknowledgements
The authors acknowledge Chirag Patel, MD, PhD and Mason Pearce-Clawson, BS who provided early technical assistance. The study was funded in part by the Patricia L. Unger Fund of Berks County Community Foundation, and the Paul and Anna Shockey Family Fund. This research did not receive any specific funding from agencies in the public or commercial sectors.

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