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REVIEW ARTICLE

A Review of Factors Influencing Anxiety and Depression in Persons with Multiple Sclerosis during the COVID-19 Pandemic

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ABSTRACT

Patients with multiple sclerosis have been subjected to extra levels of stress during the COVID-19 pandemic when they were singled out by governmental regulatory agencies as sufficiently immune-compromised persons that should be in the first group to receive the untested, new COVID-19 vaccine. The designation of these persons in such a high-risk group compounded their anxiety and depression. Early in the disease in 2020-2021, little was known about the disease, the vaccine, or whether their disease-modifying therapies for multiple sclerosis were subjecting them to more immunomodulatory suppression. This review is not comprehensive of all articles written on COVID-19 and multiple sclerosis, but selectively looks at research on COVID-19 and use of low-doses of naltrexone as treatment. Specific causes for anxiety and depression are discussed in light of evidence that suggests that the length of disease, rather than age, sex, or therapy leads to more anxiety. Low-dose naltrexone in combination with other disease-modifying therapies, or alone, reduced the perceived levels of anxiety. These data suggest that clinicians may want to prescribe low-dose naltrexone for early-stage multiple sclerosis patients.

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune-mediated neurological disorder that negatively affects the quality of life of persons diagnosed with the disease. Based on estimates from the National Multiple Sclerosis Society, MS impacts nearly 1 million persons in the United States alone and nearly 3 million worldwide[1]. MS is a life-long disease that impacts the sensorimotor, cognitive, and psychiatric modalities and leaves many persons with MS (PwMS) to question their physical and mental quality of life and their ability to enter or stay in the workforce. This reduced quality of life often leads to anxiety and depression which are not readily treated by the current FDA-approved disease-modifying therapies (DMTs) prescribed by the neurologist.

The recent COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) resulted in many PwMS re-evaluating their treatments and side-effects in light of possible increases in risks from vaccination, worsening of MS, or even other diseases[2]. During the early months of the pandemic when COVID-19 treatments and vaccines were not yet available, PwMS had no option but to isolate. Late in 2020 and throughout 2022, when the COVID-19 infection was still considered a "pandemic" and not an "epidemic", PwMS was considered to be at high risk for contracting other diseases and/or more severe symptomatology[2-4]. Possible complications included severe respiratory distress syndrome, long-term COVID-19, and even shortened life-spans. PwMS who were prescribed anti-CD20 disease-modifying therapies (DMTs) were warned of the potential side-effects and risks from complications of the SARS-CoV-2 infection[3-6]. At that time, the Center for Disease Control and Prevention announced that persons on immunomodulatory therapies were at a higher risk for contracting the disease than others[2,6]. When vaccines became available, the Center for Disease Control and Prevention indicated that PwMS and others that were prescribed immune-modulating therapies should be in the first group to receive the vaccine regardless of their age[2]. With the level of uncertainty in both the vaccine and the future directions of the disease, more anxiety and depression compounded the list of comorbidities for PwMS[6-10].

A PubMed search in April 2023 listed more than 3000 publications discussing the pandemic and anxiety; nearly 2000 publications cited the pandemic and depression. Only a few publications, including our own, included low dose naltrexone (LDN) as a viable remedy for the anxiety and depression associated with the pandemic. LDN is a repurposed FDA-approved drug that can be offered to PwMS for treatment of fatigue or other side-effects of the disease. This review looks at the use of LDN as one of the possible therapies for MS during the COVID-19 pandemic, and whether its use reduced anxiety or depression in PwMS.

COVID-19 risks related to disease-modifying therapy

Within a year of the COVID-19 outbreak, reports indicated that PwMS were in a quandary related to signing up for the vaccine based on their personal levels of immunogenicity and the relatively unknown efficacy of the vaccine[3-7]. An excellent review by Capone and colleagues reported in a 2023 meta-analysis of COVID-19 review articles that vaccination for COVID-19 is safe for PwMS irrespective of the vaccine class – mRNA or protein[3]. Despite numerous reports on the safety of the vaccines[2,4], some PwMS still demonstrated resistance to vaccination dependent on their DMTs[5-10]. Some publications recommended that all PwMS take the vaccine, even though at that time, there was little long-term evidence on the safety or efficacy of vaccines[3]. DMTs are known to modulate the immune system, and some DMTs placed individuals at high risk for infection by reducing their humoral response and B-cell defenses. Studies looking at PwMS in Italy, Iran, and United States[5-8] cited that the particular therapy assigned to the individual was the greatest concern. Other studies[9,10] focused on the psychological state of individuals with multiple sclerosis suggesting that perhaps not taking the vaccines would lessen anxiety. Using a large world-wide data set generated by IBM in 2020, Reder and colleagues[8] reported that comorbidities and ethnicity, but not age, were strong predictors of acquiring COVID-19 infection, and that if PwMS were not of the ethnicity and age cited in his review, vaccines were not warranted. Data showed that individuals taking interferon-inducing treatment such as Copaxone® had reduced COVID-19 risk whereas anti-CD20 therapies like Ocrevus® increased the risk for COVID and/or reduced the efficacy of vaccination[8], whereas age and sex were not related. Analyzing data from an Italian cohort of more than 1300 PwMS, Sormani[5] reported that the risk of COVID-19 was two-fold higher than the normal population in a high-risk group of PwMS. The high risk group included those participants with increased hospitalization and ICU admission. In the group with the lowest rate of hospitalization, the risk increased if taking anti-CD20 treatment, but not interferon-based DMTs[5]. In summary, most reports

showed that the safety and efficacy of vaccination for PwMS approached normal levels, and only a small fraction of individuals were at increased risk. An important consideration for these individuals with lower risk for contracting COVID-19 was their mental state. The mental 'acceptability' of taking the vaccine influenced the results.

As the COVID-19 pandemic continued into 2021 and early 2022, feedback from PwMS who had continued exposure to anti-CD20 or sphingoside-1-phosphate receptor modulating treatments like Gilenya® (fingolimod) and Mayzent® (siponimod) suggested that these PwMS had reduced B-cell responses. It was noted that in PwMS higher humoral response and seroconversion are predictors of better response to vaccines[6] rather than specific DMTs. Assessing a small population of PwMS in Tehran who had MS for 10 years or less, and were in their 30's, Alirezael[9] found that the level of education and number of relapses or hospitalization events during the active period of the pandemic had impacted the health of PwMS more than the type of treatment[9]. Interesting, marital status had a small, but significant, effect[9]. Self-reported anxiety in this population with low educational background was high, but only 3.2% had severe anxiety as defined as an 8 or higher on the HADS scale[9]. Fear of the disease, and increased score on the Expanded Disability Status Scale (EDSS) which is a functional scale of physical disability with MS, and reduced employment played a role in the anxiety scores[9]. Again, the mental status of the PwMS appeared to be more important than education and age.

Increased anxiety related to length of disease

More reports were published indicating that PwMS had increased anxiety regardless of their DMT. Confusion in these data prompted us to propose a clinical study on a small population of PwMS in central Pennsylvania. Participants with a confirmed diagnosis of MS were recruited and consented December 2020 through July 2022. The research study was approved by the Penn State University College of Medicine Institutional Review Board. Our hypotheses focused on factors that altered the patients' perceived levels of anxiety and depression. It is known that more females than males have MS, and predictably, 118 of the 150 respondents (79%) were female. The study involved returning completed surveys on anxiety, depression, and a demographic page on DMTs, length of disease, and any previous COVID-19 positivity and symptoms. The Hospital Anxiety and Depression Scale (HADS) surveys[11] were previously vetted and reported feelings within the previous week. Our focus was whether immune-modulating drugs, increased the anxiety associated with COVID-19, or whether age, the length of time the person had MS, or COVID-19 positivity altered perceived anxiety and depression[12]. PwMS reported higher levels of anxiety than the general public with upwards of 17% admitting to at least one major depressive episode[11].

In our study, the response rate was 26% for mailed surveys and higher for those who completed surveys during the regularly schedule appointment at the Neurology Clinic. No significant differences were noted in the ages between males and females; the ages ranged between 18-76 years. However, the mean length of time that females had MS was almost 17 years whereas for males the length of disease ranged from 1- 57 years with a mean length of disease of nearly 18 years[12]. We noted that overall mean anxiety scores as measured on the HADS surveys were greater than 6 (out of 21) for females which was significantly higher than the mean score for males (4.5). When only the anxiety scores greater than 8 (considered to be a high "anxiety" score[11]) were considered, males and females scored comparably (~10 out of 21). The mean scores for perceived depression based on the HADS questionnaire were less than anxiety (~4 out of 21), with no significant differences in men and women. Another measure of depression, the MS-BDI questionnaire[13] revealed that depression scores were ~5 (out of 36) for females and significantly less (~2.5) for males; approximately 30 of the 150 surveys indicated that depression was substantially high (MS-BDI score of 11). The MS-BDI scale was designed to be a sensitive measure of self-reported depression specifically for PwMS, which might explain the observed sex differences for this measure that were not observed for the HADS-D survey[13].

Low-dose naltrexone reduces anxiety related to COVID-19

Analysis of our clinical data between 2020 and 2022 revealed that a subset of individuals indicated that they were not taking any FDA-approved therapeutics. Some of these individuals were taking LDN along with, or without, any disease-modifying therapy[14]. In many cases these individuals stated that they were taking daily tablets of LDN to ward off fatigue. In a substudy, comparison of anxiety and depression in PwMS taking LDN or other oral medications (because LDN is taken orally), revealed that the PwMS taking LDN had lower scores of both anxiety and depression than those persons taking only oral DMTs[14]. Although both cohorts had

small sample sizes, one may assume that DMTs involving other routes of administration would show the same pattern suggesting that LDN offered some level of protection from anxiety and/or depression. Because LDN has been shown in animal models to bind to the Opioid Growth Factor Receptor (OGFr) for approximately 6-8 hours and to result in a biofeedback mechanism that upregulated secretion of endogenous neuropeptides such as β-endorphin and [Met^5]-enkephalin (i.e., OGF)[15], it is hypothesized that the same mechanism works in humans[15,16]. Clinical studies from our laboratory have demonstrated that levels of endorphins and enkephalins are diminished in PwMS[16-19], and thus the cytokine storm that occurs with a MS relapse, or is feared with vaccination, overwhelms the immune system leading to immunocompromised immunity. Long-term exposure to LDN has been shown to offset fatigue of several diseases, and to result in better overall perception of mental and physical health[16-18]. Patel[18] reported that OGF and LDN have therapeutic effects, but that they also may be involved in macrophage activation, microglial activation, and peripheral inflammation in the murine model of MS, experimental autoimmune encephalomyelitis (EAE). Depending on whether treatment of EAE began at the time of induction of disease (prophylactically) or when the first signs of disease appeared (therapeutically), researchers noted that prophylactic treatment with LDN or OGF delayed the onset of clinical signs and suppressed neutrophil counts and lymphocyte proliferation[20]. OGF, but not LDN, had substantial effects if given at the time of disease onset, essentially reversing declining clinical behavior[20]. OGF and LDN reduced activation of microglia, but only prophylactic treatment altered CNS macrophage activation[20]. In humans, Ludwig et al. reported that serum OGF (i.e., [Met^5]-enkephalin) levels were lower amongst PwMS relative to subjects without MS[16]. Mice inoculated with myelin oligodendrocytic glycoprotein to induce EAE also had reductions in OGF within a week. LDN appeared to restore both human and mouse levels with a few days of treatment[16]. PwMS taking LDN alone or in combination with other DMTs (i.e., Copaxone) had significant reductions in levels of serum IL-6 and increases in the anti-inflammatory cytokine IL-10 expression[19].

Clinical trials and manuscripts have recently reported that 1 to 4.5 mg naltrexone per day is effective in treatment of pain, cognitive decline, and fatigue associated with several autoimmune disorders[21-30]. Despite the lack of well-controlled, matched, randomized clinical trials in the US, LDN is used worldwide for Crohn's disease[22-23], fibromyalgia[24-27], and chronic pain[28-30]. Patients with corneal neuropathic pain are able to tolerate the pain if taking LDN[30].

Only a few reports are available (as of April 2023) indicating that LDN is used for treatment of side-effects of COVID-19[14,31-33]. Pitt[31] examined the efficacy of LDN for both the prophylactic and therapeutic effects of thrombosis in COVID-19. Because LDN targets the immune system, daily administration seemed to reduce IL-1, TNF-α, and IFN-γ. Because of the evidence that LDN suppressed the cytokine storm of elevated pro-inflammatory cytokines, LDN was a potential therapy to reduce the viral load of COVID-19 (ref 15). With specific attention to the mechanism of thrombosis, LDN demonstrated efficacy at reduction of Toll-like receptor mediated inflammation and formation of fibrinogen or platelet aggregation. Choubey and colleagues reported that LDN acted to disrupt important docking of the virus to the angiotensin converting enzymes and thus dampening the inflammatory response[32], thus making LDN a possible target treatment for viral infection.

A few studies reported on the safety and efficacy of LDN in the treatment of long-covid disorders[33]. Looking at therapeutic LDN treatment of persons indicating that they had symptoms related to COVID-19 for more than 12 weeks after initial infection. Nearly a year after the initial COVID-19 diagnosis, improvement was noted in energy levels, pain levels, sleep disturbances, and concentration when taking LDN for 2-months. The betterment of mood was noted, but did not reach significance.

The use of LDN to offset anxiety and depression in PwMS is only beginning to receive scientific attention. There is a strong need for randomized, large clinical trials, with controls, to determine that LDN combats depression. Mischoulon[34] reported substantial decreases in the Hamilton Depression Rating Scale for persons on LDN in comparison to placebo-controls.

Conclusions

Reputable reports on the use of LDN to treat depression and/or anxiety emanating from COVID-19 are few[14]. Our small cohort of PwMS revealed that those taking LDN had self-reported lower scores for anxiety and depression in comparison to those on only oral FDA-approved therapies. Although the pandemic has now resolved to being called an "epidemic", the evidence that PwMS have more anxiety and depression early in their disease diagnosis should

prompt physicians to provide more psychological therapy and to monitor patients more closely during the first 5 years or so of their diagnosis. More data are required before there is a confirmatory statement made about DMT and vaccination. Evidence for "long-COVID" should also be closely monitored in PwMS as increases in anxiety and depression may be associated.

Conflict of Interest Statement
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