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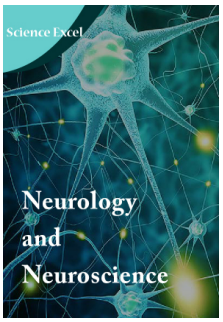

Length of Disease More than Therapy Impacts Anxiety and Depression in Multiple Sclerosis

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Abstract

Persons with multiple sclerosis (PwMS) often report a reduced quality of life related to their anxiety and depression associated with the biological unknowns of MS. The COVID-19 pandemic increased the risk of anxiety due to the uncertainties related to vaccine efficacy and immune-suppressing disease-modifying therapies. PwMS were recruited from the Neurology Clinic of the Penn State Hershey Medical Center and asked to complete a demographic questionnaire and surveys on depression (MS-Beck Depression Inventory, MS-BDI) and the Hospital Anxiety and Depression Scale (HADS). The rationale for the study is to determine whether treatment modalities, age, and length of disease impacted anxiety and/or depression in PwMS. Data from 150 participants were included in the analyses. The overall mean age was 54.6 years with a 3.7:1 female:male ratio and mean length of disease of approximately 17 years. Mean scores of the HADS-D, and high scores (> 8) were 4.68 ± 0.3 and 10.0 ± 0.32, respectively, with no differences between males and females. The mean HADS-A score was 6.15 ± 0.36 with significant differences recorded between male and females. The mean high HADS-A score was 10.77 ± 0.40, with no differences between sexes. The mean MS-BDI score was 4.15 ± 0.7 with no differences between males and females. Analyses of anxiety scores in relationship to length of disease revealed no differences between males and females. Anxiety scores did not differ for PwMS on different disease-modifying therapies. In conclusion, the number of years that PwMS had the disease impacted anxiety levels more than the age or treatment regimen..

Introduction

Multiple sclerosis (MS) is a chronic neurological illness that impacts nearly 1 million individuals in the United States [1]. The reduced quality of life related to the extended timeline of MS may lead to anxiety and depression. In 2020, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) caused a widespread infectious disease leading 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 the disease, and subsequently persons with MS (PwMS) were placed in the first group to receive vaccines regardless of age [2]. Numerous reports appeared in the scientific and public domain related to the impact of COVID-19 on PwMS [3-5]. The combination of high risk status due to MS immunomodulatory therapies, concern about infection leading to neglected care, and perhaps less direct access to clinical support because of increased telemedicine during the pandemic, led PwMS to report an increased anxiety and depression during the pandemic [3,4]. Conflicting studies have indicated increased morbidity from COVID-19 in the MS population [6] and that individuals on interferon treatments seemed to have less COVID-19 related hospitalizations than those on anti-CD20 therapy [7-9].

In the United States, approximately 3% of the population suffers from generalized anxiety disorder, with upwards of 17% reporting at least one major depressive episode [10]. Amongst PwMS, mood disorders are prevalent, and anxiety and depression are common comorbidities [9]. One-third to 50% of all MS patients suffers from depression at some point in time, and more than 20% suffer from anxiety [9]. Compounding this predisposition to anxiety and depression was the fear of acquiring COVID-19 and/or lengthy hospitalizations of PwMS and their caregivers. Moreover, information suggesting that different DMTs have deleterious effects on COVID-19 susceptibility and/or response also contributed to these concerns [5-9], with anti-CD20 therapies such as Ocrevus® therapies implicated as rendering the individual more immunocompromised.

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This study was undertaken to determine anxiety and depression levels in a small population of MS patients in central Pennsylvania during the COVID-19 pandemic. The hypothesis of the study is that MS subjects who had the disease for the shortest period of time would have higher levels of anxiety and/or depression that might be compounded by COVID-19 positivity.

Materials and methods

Study design and participants

The clinical study protocol (IRB-9784) was approved by the Pennsylvania State University College of Medicine Institutional Review Board and involved the collection of data from confirmed MS patients at the Pennsylvania State Hershey Neurology Clinic between January 2021 and October 2022. A cover letter explaining the project indicated that completion of the survey was voluntary and considered informed consent. The packet included a single page requesting general demographic information (e.g., age, treatment, length of disease), as well as the status of COVID-19 testing and symptoms, and 2 questionnaires on anxiety or depression. Packets were either distributed by mail or provided at a pre-determined clinic visit. Information could be returned to the study coordinator, or returned in the stamped, addressed envelope. There were no identifying codes assigning the surveys to specific individuals and thus follow-up was not possible. The catchment area encompassed several counties in central Pennsylvania with a total population of approximately 1.3 million and approximately 4500 individuals diagnosed with MS.

Anxiety was measured by the Hospital Anxiety and Depression Scale (HADS) that provides a reliable self-assessment for self-identified anxiety (HADS-A) or depression (HADS-D) in the previous one week [11]. In each subscale there are 7 items to be scored 0-3. Scoring ≥ 8 out of 21 was considered indicative of anxiety or depression [12,13]. A more targeted questionnaire, the Multiple Sclerosis Specific Beck Depression Inventory (MS-BDI), shown to be highly sensitive and specific to depression in multiple sclerosis was included in order to confirm levels of depression in PwMS [14].

Statistical analyses

Surveys were scored by multiple individuals and data manually entered onto spreadsheets. Mean values as well as values ≥ 8 on HADS-A, HADS-D, and MS-BDI assessments were analyzed separately. All data were analyzed using GraphPad Prism 9.4 (GraphPad Software, San Diego). Parametric data (e.g., age, length of disease) were analyzed using two-tailed t-tests or analysis of variance with post-hoc Tukey's multiple comparison tests as appropriate. Non-parametric data (e.g., survey scores) were analyzed using the Mann-Whitney test with Gaussian approximation. Correlation (two-tailed) and contingency tests (chi-square, Fisher's exact probability) were also applied. For all analyses, p values of less than 0.05 were considered significant..

Results

All study procedures were followed in accordance with the Office of Research Protections, Human Subjects Protection Office, and The Pennsylvania State University College of Medicine.

Table 1. *Demographics of all respondents*

	Age, yr	Length of Disease, yr
Female (range)	53.5±1.2 (n=115) (18-76)	16.6±1.0 (n=114) (1-46)
Male (range)	58.5±2.0 (n=32) (41-75)	17.8±1.9 (n=27) (1-57)

Data represent means ± S.E.M. No statistical differences were noted between groups.

Table 2. *Scores on HADS-A, HADS-D, and MS-BDI questionnaires for PwMS*

	HADS-A	HADS-D	MS-BDI
Female	6.60±0.40 (n=113)	4.90±0.35 (n=112)	4.79±0.48 (n=110)
Anxiety or depression	10.78±0.43 (n=45)	9.90±0.34 (n=28)	11.89±0.83 (n=28)
Male	4.48±0.80 (n=31)*	4.00±0.60 (n=32)	2.52±0.60** (n=29)
Anxiety or depression	10.38±1.35 (n=8)	11.50±2.60 (n=4)	11.00±1.00 (n=2)

Data represent means ± S.E.M. and were analyzed using two-tailed t-tests between males and females for each category. Independent two-tailed t-tests were conducted on summed scores ≥ 8 on each subscale in order to determine "anxiety" or "depression" [12]. Significantly different from mean female scores in the same category at $p<0.05$ (*) pr $p<0.01$ (**).

Demographics of PwMS

155 surveys were returned by October 2022, of which 150 surveys had sufficient information to be included in the analyses. In some cases, information on a specific demographic or survey was not provided resulting in unequal n values. General demographics are presented in Table 1. The gender ratio for all respondents was 3.7:1 female to male. Mean overall age was 54.6 ± 1.1 years, and for males (n=32) 58.5 ± 2 years with a range of 41 to 75 years. Mean age for females (n=118) was 53.5 ± 1.2 years with a range of 18-76 years; values did not differ between the sexes. The length of disease for all PwMS was 16.8 ± 0.9 years; the length of disease did not differ between males and females, and ranged from 1 to 50 years.

Sex differences and length of disease relationships of overall anxiety and depression

Analyses of anxiety and depression surveys by sex indicated that females had significantly overall higher scores than males (p=0.02) on the HADS-A survey and the MS-BDI questionnaire (p=0.03) (Table 2). No significant difference was noted on HADS-D survey scores between male and female PwMS. There was a significant difference (p=0.009) in HADS-A scores between females with MS for less than or equal to 15 years (7.15 ± 0.5) in comparison to female PwMS who had the disease for longer than 15 years (5.24 ± 0.55). Scores on the HADS-D or MS-BDI surveys did not differ for either sex when analyzed based on the length of disease.

Total scores of greater than 8 on the HADS-A and HADS-D surveys are considered indicative of "anxiety" or "depression", respectively [12,13]. Evaluation of scores greater than 8 indicated no differences between male and female PwMS recording summation scores > 8 (Table 2). The proportion of responders with high scores (> 8) in each of the anxiety or depression surveys was also evaluated by two-tailed contingency tests. No significant differences were found in the proportion of scores that were considered high for the HADS-A or HADS-D surveys, but there was a significant increase in the proportion of females that had high scores on the MS-BDI test (p=0.04; Fisher Exact Probability) relative to the proportion of males with high scores. 19.1% of females, in comparison to 1.5% of males, had high MS-BDI scores.

Correlational analyses revealed that mean HADS-A scores correlated with mean MS-BDI scores (r2 = 0.5513; p<0.0001) and HADS-D scores (r2 = 0.4451; p<0.0001); mean HADS-D correlated with MS-BDI scores (r2 =0.5745; p<0.0001). High scores (> 8) on HADS-A questionnaires correlated with mean MS-BDI scores (r2 = 0.428; p<0.0001) and with "depression" as indicated by high scores on HADS-D surveys (r2 = 0.185; p=0.0018). High scores on the HADS-D survey correlated positively with scores on the MS-BDI test (r2= 0.2536; p=0.0046). When responders were divided into groups based on whether their length of disease (LOD) was greater than 15 years vs less than or equal to 15 years, there were no significant differences in the LOD for males or females, thus the sexes were combined for further evaluation. Scores on the HADS-A questionnaire were significantly (p=0.0095) higher (mean= 7.15) for those with LOD less than or equal to 15 years, in comparison to a mean score of 5.2 for LOD greater than 15 years (Table 3). No significant differences were recorded relative to LOD and HADS-D and MS-BDI scores. Analyses to identify any relevant correlations between length of disease and anxiety or depression revealed that LOD did correlate with HADS-A scores for all PwMS, with higher scores being associated with shorter disease duration (r2=0.07; p=0.001; n=137). LOD and mean HADS-D or mean MS-BDI did not correlate significantly.

Table 2. *Scores on HADS-A, HADS-D, and MS-BDI questionnaires for PwMS*

	HADS-A	HADS-D	MS-BDI
LOD ≤ 15 yr	7.26±0.48	4.73±0.42	4.48±0.53
LOD > 15 yr	5.51±0.55**	4.61±0.45	4.27±0.65

Values represent means±SEM. Data were analyzed using two-tailed t-tests. Significantly different from LOD ≤ 15 years at p<0.01.

Table 4. *Anxiety and depression scores for PwMS categorized by disease-modifying therapy (DMT)*

	Oral Therapy	Self-injected Therapy	IV Infusion
HADS-A	4.11±0.68 (n=36)	5.57±0.82 (n=28)	3.75±1.45 (n=8)
HADS-D	5.17±0.72 (n=36)	4.43±0.83 (n=28)	3.00±0.96 (n=8)
MS-BDI	3.18±0.69 (n=33)	3.44±0.77 (n=25)	2.38±1.56 (n=8)

Values represent means ± S.E.M. Oral therapies include Aubagio®, Tecfidera®, S1p modulators, and Mavenclad®. Self-injected therapies included Copaxone®, interferons, and Kiesimpta®. IV infusion therapies included Tysabri® or Ocrevus®. There were no significant differences between DMTs for each behavioral assessment.

Different disease-modifying therapies resulted in differences in anxiety and depression

With regard to disease modifying therapy, because of the small N values for each specific therapy, data on anxiety and depression scores relative to DMTs were collectively analyzed based on their route of administration (Table 4). Three groups of therapy were established including intravenous drugs such as Tysabri®/natalizumab, Ocrevus®Ocrelizumab, oral medications such as Aubagio®/terifludimide, Tecfidera®/fumerates, Gilenya®/fingolimod, Mavenclad®and self-injected DMTs including Copaxone®/glatiramer acetate, interferons (Rebif®/Avonex®/Plegrity®), and Kiesimpta®. A fourth group comprised of individuals that indicated either no treatment or low dose naltrexone (LDN) only and data from those patients were not included in this analysis. Assessment was made regarding HADS-A scores in relation to the DMTs that PwMS were taking in addition to reported previous COVID-19 positivity. There were no significant differences in mean HADS-A scores for COVID+PwMS when evaluated by method of treatment (ANOVA F=2.195 [df 2,111] F=0.5703 Brown-Forsythe test). Also, there were no significant differences in HADS-D scores when evaluated by method of treatment (ANOVA F=0.35 [df 2, 111]= 0.4655 Brown-Forsythe test). In addition, there were no significant differences in MS-BDI scores (F=1.76 [df 2,106]). When data were corrected for the Bartlett's test, a significance of p=0.017 was noted. No significant differences were found in the mean HADS-A, HADS-D, or MS-BDI scores for the total PwMS on DMTs. However, it should be noted that mean HADS-A scores for males (1.7 ± 0.42) taking no DM (n=7) had significantly lower scores than females (6.1 ± 3.1) taking no DMT (n=15) (p = 0.05, two-tailed t-test).

For each DMT, the number of PwMS who were considered to have "anxiety", i.e., HADS-A >8, were as follows: Copaxone® (41.4%), fumarates (38.9%), Aubagio® (100%), Mavenclad® and Ampyra® (50%), Tysabri® (36.4%); the remaining DMTs had fewer than 35% with anxiety. Of interest, no PwMS taking LDN only had scores indicative of anxiety

Effects of COVID-19 testing on anxiety and depression

A subgroup of PwMS who indicated that they had tested for COVID was analyzed for anxiety and depression (Table 5). Eighty-seven individuals tested for COVID-19 and of those, 37% tested positive. The sex ratio for those tested for COVID-19 was 3.7:1, female to male. Eight males and 24 females tested positive and 10 males and 42 females tested negative. The mean age and LOD for PwMS who tested for COVID is presented in Table 3. The mean age of all COVID+ individuals was 52 years, and for COVID- subjects was 54 years. Mean age of COVID+ females was significantly less than that of COVID+ male individuals; the mean age for COVID negative individuals did not differ and ranged between 28 and 79. The questionnaire included 13 symptoms listed by the Center for Disease Control and Prevention as prominent symptoms of COVID-19, and PwMS were asked to mark as many as were appropriate. No statistical analyses were performed on symptoms, but the top 4 mentioned symptoms were fatigue (n=17), cough (n=13), loss of taste (n=12), and rhinitis (n=11).

Depression scores differed significantly between those testing positive or negative. Mean HADS-D scores were higher (p=0.049) for COVID- PwMS (5.3 ± 0.6) in comparison to those testing positive (3.72 ± 0.2). MS-BDI scores were significantly higher (p=0.013) for COVID- PwMS (5.44 ± 0.6) in comparison to those testing positive (2.64 ± 1.1). Further analyses of those testing positive revealed that HADS-A scores were significantly higher for COVID+ females in comparison to COVID+ males (p=0.0124), and no differences between male or female COVID+ persons were noted on surveys measuring depression. Moreover, there were no significant differences in HADS-A, HADS-D, or MS-BDI scores relative to a specific DMT for COVID+ individuals. Nine individuals who were COVID+ had one or more behavioral scores ≥ 8, whereas 27 subjects who were COVID- scored ≥ 8 in at least one survey. Of note, no males testing positive for COVID scored ≥ 8 on any behavioral survey, whereas 9 of 24 females had scores ≥ 8 on the HADS-A survey. Among the COVID- subjects, 3 of 10 males had anxiety scores ≥ 8 and 18 females had high anxiety values ranging from 8 to 18. Of the 26 responders who received Ocrevus®, 4 were COVID+ (15%); 1 responder receiving Kesimpta® (100%) was COVID+.

Discussion

Our data from central Pennsylvania appeared to reflect other populations of PwMS in terms of the ratio of women to men,

Table 5. *Demographics and anxiety and depression scores for PwMS who tested for COVID-19*

	COVID-19+		COVID-19-	
	Female (N)	**Male (N)**	**Female (N)**	**Male (N)**
Age, yr (Range, yr)	48.7 ± 2.8 (n=24) (18-70)	62.6 ± 4.3* (n=8) (44-75)	53.4 ± 1.9 (n=42) (28-79)	57.6±4.0 (n=10) (41-75)
LOD, yr (Range, yr)	13.2 ± 1.8 (1-32)	20.8 ± 2.8* (9-26)	15.4 ± 1.3 (1-36)	19.0±6.0 (1-57)
HADS-A	6.17 ± 0.72	2.63 ± 0.78 **	7.10 ± 0.68	6.00 ± 1.14#
HADS-D	3.92 ± 0.69	3.13 ± 0.83	5.60 ± 0.63	4.30 ± 0.96
MS-BDI	3.17 ± 0.81	1.13 ± 0.74	6.39 ± 1.07#	3.50 ± 1.09

Values represent means±SEM. Data were analyzing using two-tailed t-tests. Significantly different between males and females who tested positive for COVID-19 at p<0.05 (*) or p<0.01 (**). Significantly different between the same sex of COVID+ and COVID- cohorts at p<0.05 (#).

LOD, and age [8,9]. Moreover, the surveys indicated that anxiety, more than depression, was a substantial factor. Female PwMS had higher anxiety scores, supporting earlier reports of sex differences in anxiety scores [9]. In general, the length of disease did not impact depression scores, and specific DMTs had little effect. The length of disease did correlate with higher anxiety for PwMS who had shorter periods of diagnosis (≤ 15 years) in comparison to those with MS for longer than 15 years.

Given that the clinical study began early in the pandemic, the relationships between COVID-19 positivity, anxiety and depression are tenuous. Previous COVID-19 positivity was linked to depression more than anxiety, with COVID-19- persons indicating more depression than COVID-19+ persons. However, amongst the group of COVID-19+ persons, anxiety scores were significantly higher for females than males, with no differences in depression scores noted. These data support and extend previous data on relationships between MS length of disease, DMTs, and COVID-19 on anxiety and depression. Meta-analyses of PwMS from Iran indicated that persons treated with anti-CD20 antibodies were more likely to have COVID-19 (or symptoms) [8]. Our data corroborated these data by indicating that glatiramer acetate, dimethyl fumarate, and interferon-based DMTs did not predispose patients to COVID-19. The 3 anti-CD20 therapies of concern are rituximab (Rituxan®), ocrelizumab (Ocrevus®), and Ofatumumab (Kesimpta®).

In a report of 282 participants, Alirezzaei et al. [9] showed that approximately 3% of respondents had high levels of anxiety and a fear of COVID-19; mean length of disease, which was approximately 7 years, did not affect scores. Reports on increased prevalence of depression during the COVID-19 pandemic suggest that a potential causative agent is the unknown nature of the disease [7,9]. In a review of 28 published reports evaluating risk and immunity, Etemadifar et al. [8] concluded that, based on the literature review, most DMTs did not alter the percent sero-conversion rates in PwMS following mRNA vaccinations. However those receiving anti-CD20 or SiPRM DMTs did have substantially lower humoral immunity following vaccination.

Sormani et al. [3] reported that there was an increased risk among PwMS to report more severe symptoms, more hospitalizations, and more deaths related to COVID-19 than the general Italian population. Although data was stratified by DMTs, Ocrevus® and interferon-taking patients had lower incidence (10.9 and 9.8%, respectively, of severe disease course relative to those receiving dimethyl fumarate (17.5%), natalizumab (13.78%) or fingolimod (12.2%).

Only a few reports on anxiety and depression evaluations during the pandemic in PwMS have been published. Ramezani et al. [7] evaluated an Iranian population and determined that the percentage of PwMS scoring high on the HADS-A (31%) and HADS-D (39%) subscales increased from previous studies, but specific information was not provided. This group found no correlation with anxiety/depression and sex, drug abuse, smoking or positive COVID-19 tests. Another report examined a population in Tehran and found that overall prevalence of depression symptoms was 51.4% higher than the general population and was in part due to the fear of COVID-19, marital status, level of education, and previous hospitalizations due to MS relapses (correlated with anxious symptoms in a univariate analysis) [9]. Reder et al. [5] compared the records of PwMS and those with lupus using the Biogen Global Safety Database, and concluded that comorbidities, obesity, and race, more than age, were related to a higher risk of COVID-19 infection. Interferon-based DMTs and glatiramer acetate were associated with reduced COVID-19 risk; anti-CD20 DMTs showed an increased risk in this sample population in 2020 and 2021.

In conclusion, our data are consistent with larger meta-analyses but demonstrate new findings that the length of disease more than the therapeutic approach confers greater anxiety on PwMS. While female PwMS seem to be more prone to anxiety, male PwMS with a shorter length of disease had high scores on the questionnaires. This subpopulation of patients should be provided validated information from publications showing that MS itself, or the DMTs recommended, are not risk factors, and rendering individuals susceptible to COVID-19.

Limitations of the present study are related to the regional sample population from central Pennsylvania as well as the fact that the study was conducted early in the COVID-19 pandemic. The surveys were not ear-marked to specific individuals and follow up to determine if the subject ever developed COVID-19 was not feasible. Furthermore, data on severity or length of COVID disease as well as the status of vaccination were not obtained.

In conclusion, the data reveal that individuals recently diagnosed with MS, and likely other neurodegenerative disorders, should be carefully monitored for early signs of anxiety and/or depression in order to begin relevant mental health treatment.

Conflicts of interest

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.

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References

1. National Multiple Sclerosis Society. Multiple sclerosis & COVID-19. https://www.nationalmssociety.org/coronavirus Updated August 2022.
2. Centers for Disease Control and Prevention (2019) People with certain medical conditions. Avaialable at https://www.cdc.gov/coronavirus/2019-ncov/your-health/understanding-risk.html?CDC_AA_refVal=https%253A%252F%252Fwww.cdc.gov%252Fcoronavirus%252F2019-ncov%252Fneed-extra-precautions%252Findex.html. Accessed January 2023.
3. Sormani MP, Schiavetti I, Carmisciano L, et al. COVID-19 severity in multiple sclerosis. Neurol Neuroimmunol Neuroinflamm. 2022;9:e1105.
4. Zheng C, Kar I, Chen CK, et al. Multiple sclerosis disease-modifying therapy and the COVID-19 pandemic: Implications on the risk of infection and future vaccination. CNS Drugs. 2020;34:879-896.
5. Reder AT, Centronze D, Naylor ML, et al. COVID-19 in patients with multiple sclerosis: associations with disease-modifying therapies. CNS Drugs. 2021;35:317-330.
6. Berger JR, Brandstadter R, Bar-Or A. COVID-19 and MS disease-

modifying therapies. Neurol Neuroimmunol Neuroinflamm. 2020;7:e761.

7. Ramezani N, Ashtari F, Bastami EA, et al. Fear and anxiety in patients with multiple sclerosis during COVID-19 pandemic; report of an Iranian population. Mult Scler Rel Dis. 2021;50:102798.
8. Eternadifar M, Nouri H, Pitzalis M, et al. Multiple sclerosis disease-modifying therapies and COVID-19 vaccines: A practical review and meta-analyses. J Neurol. Neurosurg Psychiat. 2022;93:986-994.
9. Alirezaei M, Eskandareih S, Sahraian MA, Noghadasi AN. Depression, anxiety, and fear of COVID-19 in patients with multiple sclerosis in pandemic era: a cross-sectional study. Neurol Sci. 2022;43:59-66.
10. Anxiety & Depression Association of America. Anxiety Disorders – Facts & Statistics. https://adaa.org/understanding-anxiety/facts-statistics. Updated October 2022.
11. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatry Scandinavia. 1983;67(6):361-370.
12. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. J Psychosom Res. 2002;52:69 77
13. Rishi P, Rishi E, Maitray A, Agarwal A, Nair S, Gopalakrishnan S. Hospital anxiety and depression scale assessment of 100 patients before and after using low vision care: A prospective study in a tertiary eye-care setting. Indian J Ophthal. 2017;65:1203-1208.
14. Strober LB, Arnett PA. Depression in multiple sclerosis: The utility of common self-report instruments and development of a disease-specific measure. J Clin Exp Neuropsych. 2015;37:722-732.