ORIGINAL ARTICLE

Impact of opium dependency on clinical and neuropsychological indices of multiple sclerosis patients

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Abstract

The aim of this study was to determine the effect of opium on clinical and neuropsychological parameters in multiple sclerosis (MS) patients with substance dependency. A cross-sectional study was conducted on MS patients in Rafsanjan, Iran. Forty opium-addict MS patients (10 males and 30 females) aged between 18 and 50 years were compared with 40 MS patients with no addiction. Word-Pair Learning, Mini-Mental State Examination (MMSE), Wisconsin Card-Sorting Test (WCST), Depression, Anxiety, Expanded Disability Status Scale (EDSS), Fatigue, and the Multiple Sclerosis Functional Composite (MSFC) were measured and compared in the two groups. The comparison of two groups showed a significant increase trait anxiety ($P < 0.001$), fatigue ($P = 0.009$) and significant decrease in the executive function ($P = 0.003$), MMSE ($P = 0.003$), and working memory ($P < 0.001$) in addicted MS. It indicates the better efficiency of processing in the non-addicted MS patients. The MSFC z-score also was significantly higher in the non-addicted group ($P < 0.001$). The opium addiction has a negative impact on the clinical and neuropsychological outcome in MS patients.

Keywords Opium · Cognition · Multiple sclerosis · Addiction · Substance dependency

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that results in myelin destruction in the brain and spinal cord and gradually leads to loss of muscular ability [1]. This chronic progressive disease mostly occurs in 20–40 years of age and is more prevalent in women than men [2]. MS causes numerous psychological [1] and cognitive disorders in MS patients [3]. For example, verbal memory [4], information processing [5], spatial memory [6], and visuospatial memory [3, 7] have been shown to be impaired in MS patients. Although cognitive and behavioral disorders may be found in MS patients, they can also present as symptoms or side effects of opium addiction. Opioid addiction is a long-lasting (chronic) disease that can cause major health, social, and economic problems. Opioids are a class of drugs that act in the nervous system to produce feelings of pleasure and pain relief. Some opioids are legally prescribed by healthcare providers to manage severe and chronic pain [8].

It was believed that pain is uncommon in MS, but various studies have shown that it is an important symptom of MS. Of MS patients, 40–80% complain about pain including nociceptive pain, headache, and peripheral pain as well as central pain and trigeminal neuralgia [9–11]. It has also been shown that MS patients are insensitive to opioid treatment of pain [12]. This may be due to reduced number of opioid receptors in the spinal cord in MS patients [13]. On the other hand, opioids are one of the most important regulators of the nervous and immune systems and are involved in pain sensation pathways [14, 15]. The pain caused by MS can affect the quality of life, course of the disease, and treatment options [9] and therefore,

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some patients get use to opium to reduce their pain. Here, we aim to investigate the impact of opium addiction on depression, anxiety, and cognitive and clinical indices in MS patients.

Methods

Participants

This study was approved by the institutional review board and the local Ethics Committee of Rafsanjan University of Medical Sciences (No. 9/459) in Iran. MS diagnosis was based on the 2011 McDonald criteria [16]. Forty addicted and forty non-addicted MS patients from Rafsanjan multiple sclerosis association participated in the study from January to June 2016. Informed consent form was completed by all patients participated in the study.

Outcome measures

In this descriptive, cross-sectional study, both MS groups (addicted and non-addicted) underwent neuropsychological and clinical tests as follows. The DSM 5 (Diagnostic and Statistical Manual of Mental Disorders) criteria was chosen for substance dependency diagnosis and then psychiatrist approved diagnosis [17]. The length of opium use was at least 1 year. The addicted MS patients had a history of chronic opium abuse (through respiratory or gastrointestinal routes) for at least 1 year.

Word-Pair Learning

This test is mainly used to assess hippocampal function. In this task, seven pairs of unrelated words were used (for example, car-sun). The experimenter first tells all pairs and then repeats the first word of each pair and asks the patient to recall the second word of the pair. A score of 1 to 6 is given to the total number of trials needed for successful learning of all the seven word pairs, and a score of 10 is given to subjects who are unable to learn them in 6 trials [18].

The Mini-Mental State Examination (MMSE)

This is an 11-question exam that can be used to assess mental status in five cognitive functional zones: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment [19].

The Wisconsin Card-Sorting Test (WCST)

A valuable test for diagnosing the frontal lobe problems that requires certain cognitive functions to be intact such as attention, working memory, and visual processing. It measures the ability to perform certain types of abstract reasoning (especially the ability to change problem-solving strategies as needed) [20]. Seven indices were analyzed: (1) the number of categories completed (CC): overall number of times for 10 correct responses in a row; (2) the number of perseverative errors (PE): consecutive matches according to the same wrong criterion, reflecting tendency towards perseveration; (3) the number of non-perseverative errors (NPE): wrong matches that are not perseverative; 4) the total number of errors (NE): responses that are perseverative and are not correct; 5) trials to complete the first category (trial 1st): the total number of trials to successfully complete the first category [20].

The Beck Depression Inventory (BDI)

This is one of the most widely used psychometric tests for measuring the severity of depression. The Beck Depression Inventory (BDI) contains 21 items, each with a response set of four statements (0 = absent or mild, 3 = sever) describing the severity of depression symptoms over the past 2 weeks. A total score is computed by summing the scores across items (range = 0–63) [21]. We used the Persian version of this test for which validity and reliability have been demonstrated previously (Cronbach's α 0.89, test–retest correlation 0.94) [22].

The State-Trait Anxiety Inventory (STAI)

This is a measure for anxiety in adults. It is also used to make a distinction between state anxiety and trait anxiety (feelings of anxiety and depression). The State-Trait Anxiety Inventory (STAI) contains 40 questions which take 10–20 min to complete [23]. Its validity and reliability have been demonstrated in Iran previously (for state anxiety and trait anxiety, Cronbach's α 0.9084 and 0.9025, respectively, and test–retest correlation 0.945) [24].

The Expanded Disability Status Scale (EDSS)

It is the primary clinical outcome for evaluating multiple sclerosis in clinical trials. Its score ranges 0–10, with the greater degree of disability in higher scores [25].

Fatigue Severity Scale (FSS)

It measures the severity of fatigue and its effect on patient activities and lifestyles. The items are scored on a 7-point scale with, 1: strongly disagree and 7: strongly agree

Table 1 Demographic characteristics of two groups of MS patients

	Non-addicted MS group	Addicted MS group	P value
Age (year)—no. (%)			0.846
≤ 30	15 (37.5)	15 (37.5)	
31–40	14 (35.0)	16 (40.0)	
> 40	11 (27.5)	9 (22.5)	
Mean ± SEM	33.53 ± 1.53	34.18 ± 1.20	0.740
Male—no. (%)	10 (25.0)	10 (25.0)	1.000
Education—no. (%)			0.090
Elementary	5 (12.5)	4 (10.0)	
Secondary school	17 (42.5)	8 (20.0)	
High school	11 (27.5)	21 (52.5)	
College	7 (17.5)	7 (17.5)	
Duration of MS (year)—no. (%)			
≤ 2	11 (27.5)	6 (15.0)	
3–5	22 (55.0)	27 (67.5)	
> 5	7 (17.5)	7 (17.5)	
Mean ± SEM	3.75 ± 0.37	4.88 ± 0.55	0.096
Occupation—no. (%)			0.419
Employed	11 (27.5)	14 (35.0)	
House wife	15 (37.5)	10 (25.0)	
Farmer	2 (5.0)	1 (2.5)	
Unemployed	4 (10.0)	9 (22.5)	
Worker	8 (20.0)	6 (15.0)	
Opium consumption (g/day)—no. (%)			–
< 1	NA	5 (12.5)	
1–3	NA	32 (80.0)	
> 3	NA	3 (7.5)	
Duration of opium consumption (year)			
Mean ± SEM	NA	4.13 ± 0.37	–

(minimum score 9 and maximum score 63). The higher score shows greater fatigue severity [26].

The Multiple Sclerosis Functional Composite (MSFC)

It is comprising the average of the z-scores on the timed 25-ft walk, the 9-hole peg test, and the paced auditory serial-addition test (PASAT) with a 3-s inter stimulus interval, with lower degree of disability in higher scores [27].

Statistical analysis

Data are reported as mean ± SEM (standard error of mean) for numeric variables and as number (percentage) for categorical variables. Demographic characteristics were compared across the two groups of non-addicted MS and addicted MS patients using independent two-sample t test, chi-square test, and Fisher's exact test. Neuropsychological and clinical tests were compared using multivariate analysis (age, EDSS, and disease duration) in both groups of patients. SPSS version 20 was used for data analyses. The level of significance was set at 0.05.

Results

Table 1 summarizes the age distribution of the subjects, their occupation, educational status, duration of disease, duration of opium consumption, and the amount of opium consumption expressed in g/day. Within the addict MS group, it was found that 5 patients (12.5%) used < 1 g/day, 32 patients (80%) 1–3 g/day, and 3 patients (7.5%) > 3 g/day. As the duration of the disease concerns, patients were divided into three categories. There was no significant difference between groups (Table 1).

Neuropsychological results

Table 2 shows the outcome measures in addicted MS group compared with non-addicted MS group. The anxiety between the two groups was significantly different ($P < 0.001$). The

Table 2 Comparison of the neuropsychological and clinical tests in two groups of addicted and non-addicted MS patients

Assessment	Non-addicted MS group	Addicted MS group	P value*
Depression (mean ± SEM)	12.68 ± 1.61	15.59 ± 1.61	0.213
Anxiety (mean ± SEM)			
State anxiety	45.10 ± 2.33	48.72 ± 2.33	0.283
Trait anxiety	48.05 ± 1.60	58.49 ± 1.60	< 0.001
MMSE (mean ± SEM)	27.06 ± 0.40	25.33 ± 0.40	0.003
Word-pair learning (mean ± SEM)	3.85 ± 0.43	6.16 ± 0.43	< 0.001
WCST (mean ± SEM)			
CC	4.46 ± 0.19	4.83 ± 0.19	0.200
PE	2.51 ± 0.31	2.33 ± 0.31	0.691
NPE	36.49 ± 0.26	37.65 ± 0.26	0.003
NE	17.12 ± 1.28	15.67 ± 1.28	0.434
Trial 1st	6.30 ± 0.12	6.65 ± 0.12	0.057
EDSS (mean ± SEM)	0.85 ± 0.15	1.10 ± 0.15	0.268
Median (1st quartile–3rd quartile)	0 (0–2)	1 (0–2)	
FSS (mean ± SEM)	35.10 ± 2.04	43.10 ± 2.04	0.009
MSFC z-score (mean ± SEM)[#]	0.24 ± 0.12	− 0.61 ± 0.12	< 0.001

MMSE the Mini-Mental State Examination, *WCST* the Wisconsin Card-Sorting Test, *CC* the number of categories completed, *PE* the number of perseverative errors, *NPE* the number of non-perseverative errors, *NE* the total number of errors, *Trial 1st* trials to complete the first category, *EDSS* the Expanded Disability Status Scale, *FSS* Fatigue Severity Scale, *MSFC* the Multiple Sclerosis Functional Composite, *SEM* standard error of mean

*Neuropsychological and clinical tests were compared using multivariate analysis with age, EDSS, and disease duration in both groups of MS patients

[#] Scores on the MSFC are expressed as z-score, with higher scores indicating better capabilities

depression in opium-dependent MS patients was higher in comparison with non-addicted MS patients but it was not significant ($P = 0.213$) (Fig. 1). The results showed a significant difference between the two groups in the executive function (due to NPE in the Wisconsin Card-Sorting Test (WCST); $P = 0.003$) and Mini-Mental State Examination (MMSE) performance ($P = 0.003$) (Table 2). The mean score of Word-Pair Learning Test in opium-dependent MS patients was

Fig. 1 The mean depression and anxiety in both addicted and non-addicted MS patients. Data are expressed as mean ± SEM. ***$P < 0.001$
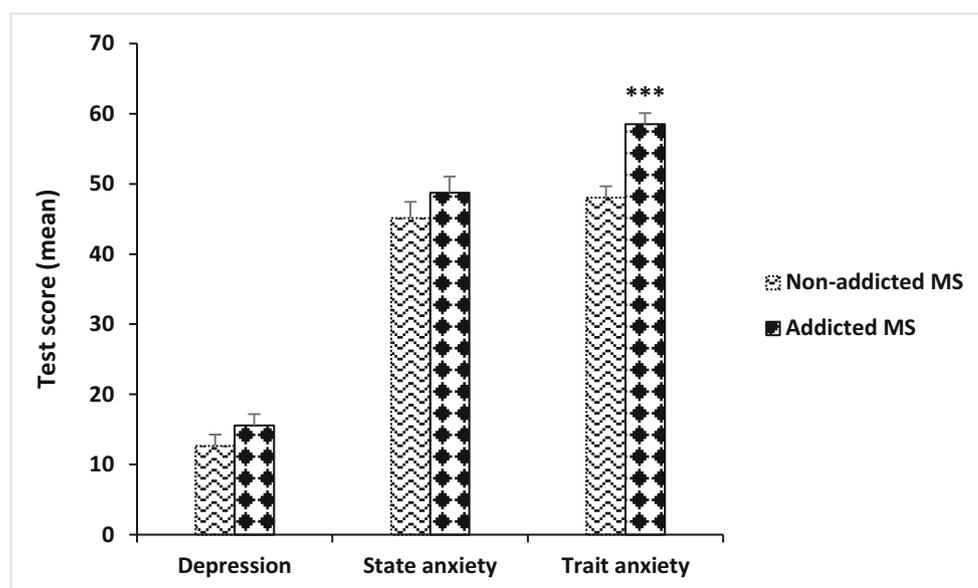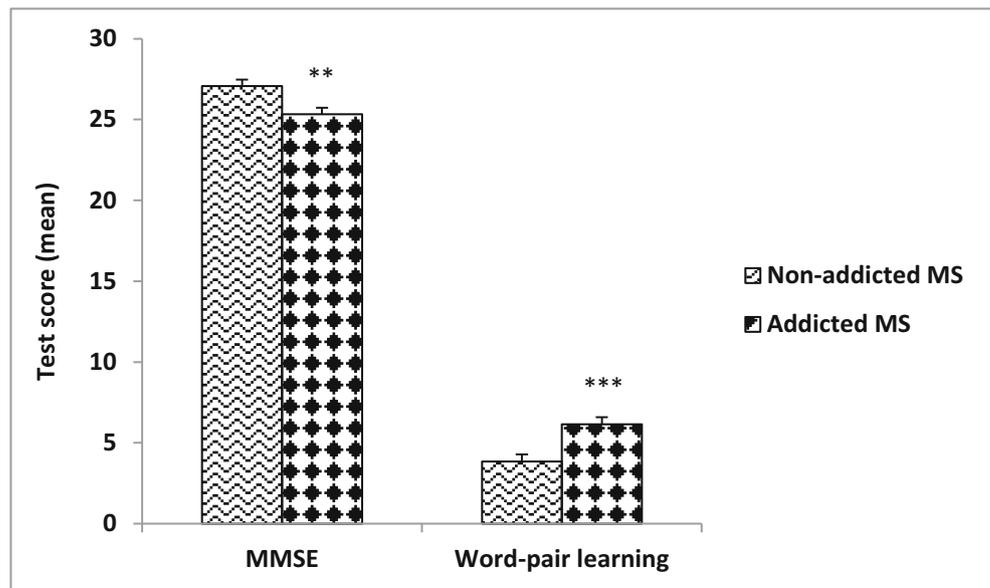
Fig. 2 The mean MMSE and Word-Pair Learning in both addicted and non-addicted MS patients. Data are expressed as mean ± SEM. **$P < 0.01$, ***$P < 0.001$
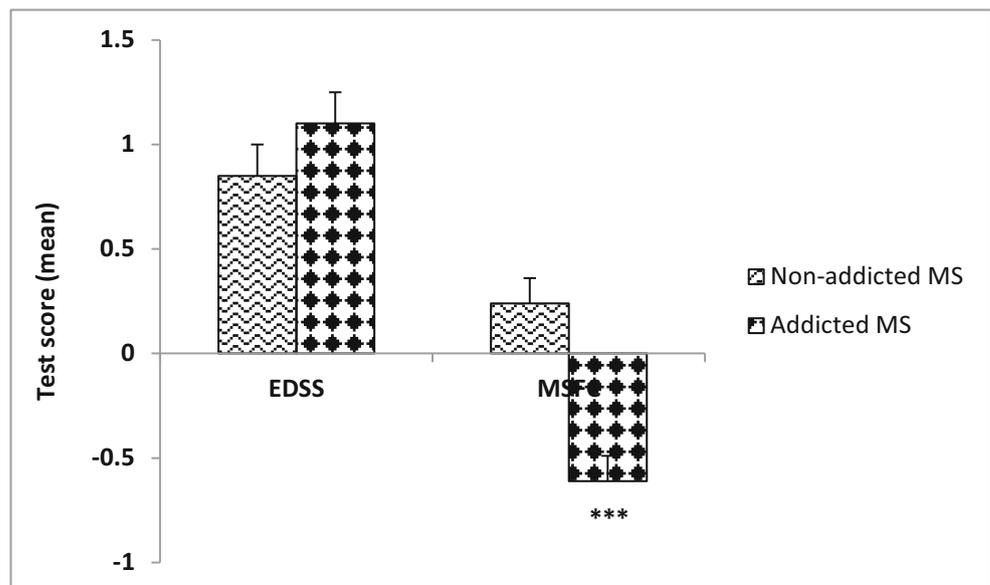

significantly increased compared with non-addicted MS group ($P < 0.001$), indicating better performance effectiveness and efficiency of processing in the non-addicted MS group (Fig. 2).

Clinical results

Data showed the Expanded Disability Status Scale (EDSS) in opium-dependent MS patients was higher in comparison with non-addicted MS patients although it was not significant ($P = 0.268$) (Fig. 3). For fatigue, we observed a significant increase in the Fatigue Severity Scale (FSS) in addicted MS patients ($P = 0.009$). The Multiple Sclerosis Functional Composite (MSFC) score was founded to be significantly higher in the non-addicted MS group compared with the addicted MS group ($P < 0.001$) (Fig. 3).

Discussion

Despite the rise in serious adverse events involving the use of opium, many patients suffering from chronic pain and various other disorders such as diabetes mellitus, hypertension, and hyperlipidemia use it. This might be due to belief of some people which originates from traditional ancient medicine. In this descriptive cross-sectional study, the results showed that the opium may cause deficits in learning and memory of addicted MS patients, compared with non-addicted MS patients. Although we found that opium addiction has significant effect on the progression of disability in MS patients, it may increase anxiety rate.

Cognitive dysfunction has a significant negative impact on the current living situation of MS patients. The results of many studies indicated that patients with MS have difficulties in

Fig. 3 The mean EDSS and MSFC in both addicted and non-addicted MS patients. Data are expressed as mean ± SEM. Scores on the MSFC are expressed as z-score, with higher scores indicating improvement in disability. ***$P < 0.001$

processing information at the level of a hypothesized articulatory loop in working memory [28–30]. We observed an increase in the MMSE and MSFC z-score among non-addicted MS patients compared with addicted MS patients, indicating that opium may have destructive effects on walking, hand function, and especially memory performance. It has been reported that morphine exposure causes loss of hippocampus pyramidal neurons in 18- and 32-day-old infant mice [31]. Also, it has been demonstrated that addiction to opioids may cause memory deficit through reduction of long-term potentiation (LTP) in the hippocampus [32]. The results of our study indicated that the rate of processing and working memory in opium-addict MS patients decreases significantly. More importantly, opium significantly affected the nature of the data fragmentation, an additional indication of deficit in the working memory performance.

Clinically significant depression can affect up to 50% of patients with MS over the course of their lifetime [33]. On the other hand, mood disorders, especially depression and anxiety, are the most common psychiatric disorders in patients who tend to use opium [34]. A major study conducted in Lebanon showed that 64.9% of patients admitted for opium dependency had various psychiatric disorders [35]. Our opium-addicted MS patients had higher anxiety scores than non-addicted MS patients. Our study showed that opium-dependent MS patients were generally more prone to some psychiatric disorders such as trait anxiety.

One of the most commonly reported complaints in MS patients, and also adverse event in opium addiction, is fatigue [26]. Our results indicated that fatigue was less in non-addicted MS patients than addicted MS patients, and this difference was statistically significant.

Conclusion

The results of this study showed that rate of anxiety, fatigue, and some neuropsychological disorders might increase following opium dependency in MS patients. Although, no significant effect on the disability progression was seen.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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