



The relationship between Restless legs Syndrome and opioid abuserelapse

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ABSTRACT

Restless Legs Syndrome (RLS) is a sensory-motor neurological disorder that overally affects about 10 percent of adults. RLS can be correlated with opioid abuse relapse and considered as a risk factor in relapse of opioid abuse. This study aimed to investigate the relationship between restless legs syndrome and opioid use relapse. In this cross-sectional study participants included 214 patients with opioid abuse referred to Tehran Psychiatric Institute for substance abuse treatment in 2015. After obtaining informed consent from patients, Restless Legs Syndrome Rating Scale applied to assess Restless Legs Syndrome severity. To determine relapse of substance abuse urine morphin test was used. The results showed that there was no significant difference statistically between patients with substance abuse relapse and patients without substance abuse relapse in terms of sex, marital status and education level ($p > .05$) while there was significant difference between the two groups in terms of age, the age of onset of drug use, way of drug consumption, family history of drug abuse and smoking ($p < .05$). Three month after the withdrawal the frequencies of mild and sever cases of RLS in group without substance abuse relapse were 66.7% and 1.3% respectively while in group with substance abuse relapse the frequency of mild and sever cases of RLS were 22.8% and 19.9% respectively which statistically was meaningful ($p = .0001$). Based on the findings of this study there was a correlation between RLS and substance abuse relapse in abusers who experienced substance withdrawal. As well as increasing the time from withdrawal the severity of this syndrome will increase.

Keywords: Opioid dependency, restless legs syndrome, substance abuse relapse

INTRODUCTION

substance abuse and dependency is a major public health problem in many countries[1]. Opioid substance abuse imposes a burden on families and health systems. Apart from its direct health and economical effects, the high costs of associated diseases such as AIDS and opioid withdrawal are considerable[2]. The main treatment method to quit opiom abuse is maintenance treatment with Methadone or Buprenorphine. The rate of opioid abuse relapse within six months after treatment has been reported more than 60%[3]. This means that a major cost of treatments is wasted due to relapse of opioid abuse, therefore identifying the cases of recurrence is important.

Restless legs syndrome (RLS) is characterized by an urge to move the legs, usually associated with limb discomfort[4]. Patients with RLS experienced involuntary and short muscular convulsions mostly in evening and

night which impairs night sleep and decreased the quality of life[5,6]. Patients with this syndrome have an irresistible desire to move the legs and describe it as unpleasant sensation that gets worse with periods of inactivity[7].The prevalence of RLS is reported as 5–10% in the normal population depending on the diagnostic criteria and the age of the population under investigation. Usually a higher prevalence is found in females comparing to males and increasing in frequency with older age[8].

Restless Legs Syndrome is a sensory-motor neurological disorder that surprisingly is common in the community, although patient and even physician awareness of it, is generally low. The causes of this syndrome are not clear. Iron deficiency and dopaminergic neuronal dysfunction in the central nervous system are thought to be the likely responsible for this syndrome[9]. Dopamine is one of the neurotransmitters involved in the pathophysiology of substance abuse[10].It seems that some of the factors associated with relapse of substance abuse are less considered.Investigating, controlling and treating these factors can help to identify people who are at risk of substance abuse relapse. The association between restless leg syndrome and consumption of some substances such as alcohol and opioid has been shown in previous studies[11,12]. Therefore these findings raise the hypothesis that restless leg syndrome can be involved in opioid abuse relapse. In this study we investigated the relationship between restless legs syndrome and relapse of substance abuse.

MATERIALS AND METHODS

This cross-sectional study was conducted on 214 patients with opioid abuse referred to Tehran Psychiatric Institute for substance abuse treatment in 2015.

Treatment included maintenance treatment with methadone and buprenorphine for two weeks.

The exclusion criteria were: age less than 18 years, dependency to other substances at the same time, any peripheral nervous system involvement such as diabetes, taking psychiatric drugs which cause movement disorders such as Akathisia, taking sedatives and GABA stimulating drugs, bipolar disorder type 1, schizophrenia and any drug-induced psychosis.

Considering the 95% confidence interval and accuracy of 0.05 and the possibility of restless legs syndrome as 0.15 based on the Cochran formula the sample size of 204 was estimated,in this study we evaluate 214 patients .The samples in this study were selected using convenience sampling.

To each subject or their guardians some information about the methods and aims of the study were given and informed consent was obtained.Two weeks after treatment onset, a demographic questionnaire that included information such as age, sex, marital status, age at onset of substance abuse, history of substance withdrawal, and psychiatric disorders, and history of psychiatric disorders in family was completed for each of the participants. To determine RLS and also its severityRestless Legs Syndrome Rating Scale (IRLS) (Investigator Version 2.2) was used at baseline and three times more (monthly). Restless Legs Syndrome Rating Scale has 10 items each scored from 0 (none), 1(mild), 2 (moderate), 3 (sever) and 4 (very severe), giving a range of scores from 0 to 40.Urine morphin test was used to determine relapse of substance abuse.

Based on clinical history, patients with and without restless leg syndrome were evaluated.Essential diagnostic criteria for RLS were: 1. an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

Data analysis performed using SPSS(V. 18). To show the quantitative variables, mean and standard deviation and for qualitative variables the frequency and ratio were used. To compare quantitative variables t-test used and comparing proportion performed with Chi 2. Multivariate logistic regression used to examine the independent relationship between variables and Restless Leg Syndrome. The level of significance was considered as 0.05.

RESULTS

Demographic data showed that there was no significant difference between patients with substance abuse relapse and patients without substance abuse relapse in terms of sex, marital status and education level ($p > .05$), but there was significant difference between the two groups in terms of age and the age of onset of substance use ($p < .05$). Also, the difference between two groups was significant in terms of way of consumption, family history of substance abuse and smoking ($p < .05$) (Table 1).

Table 1. Comparison of demographic variables between patients with substance abuse relapse and patients without substance abuse relapse

Factor		patients with substance abuse relapse (n=78)	patients without substance abuse relapse (n=136)	P-Value
Age	($\mu \pm sd$)	31.5 \pm 4.1	38.4 \pm 9.5	.0001
Age of Onset of Substance Abuse		30.1 \pm 6.4	28.1 \pm 7.3	.040
Number of Substance Abuse		1.4 \pm .5	1.3 \pm .4	.19
Duration of Substance Abuse		9.4 \pm 6.5	11.4 \pm 7.5	.064
Prescribed Dose		77.4 \pm 8	76.5 \pm 8.1	.450
Sex	Male	71(91%)	125(91.9%)	.504
	Female	7(9%)	11(8.1%)	
Marital Status	Single	7(9%)	18(13.2%)	.380
	Married	57(73.1%)	87(64%)	
	Divorced	14(17.9%)	31(22.8%)	
Education Level	Illiterate	4(5.1%)	8(5.9%)	.981
	Under School Diploma	32(41%)	58(42.6%)	
	School Diploma	28(35.9%)	48(35.3%)	
	Academic	14(18%)	22(16.2%)	
Way of Drug Consumption	Smoking	73(93.6%)	119(87.5%)	.214
	Eating	5(6.4%)	13(9.6%)	
	Injection	0(0%)	4(2.9%)	
History of treatment	No	29(37.2%)	34(25%)	.043
	Yes	49(62.8%)	102(75%)	
Family History of substance Abuse	No	34(43.6%)	44(32.4%)	.068
	Yes	44(56.4%)	92(67.6%)	
History of Minor Psychiatric Disorders	No	74(94.9%)	115(84.65)	.017
	Yes	4(5.1%)	21(15.4%)	
Smoking	No	17(21.8%)	28(20.6%)	.483
	Yes	61(78.2%)	108(79.4%)	
The Cause for Relapse	Sleep Disorder	0(0%)	30(22.1%)	.0001
	Restlessness	0(0%)	21(15.4%)	
	Excitability	0(0%)	22(16.2%)	
	Lack of energy	0(0%)	24(17.6%)	
	Lack of Motivation	0(0%)	16(11.8%)	

The frequency of RLS immediately after treatment in the group without substance abuse relapse was 88.5% and in group with substance abuse relapse was 94.9% that there was no significant correlation ($p=.39$).

One month after treatment onset frequencies of moderate cases and sever cases of RLS in group without substance abuse relapse were 16.7 % and 14.1% respectively and in group with substance abuse relapse the frequency of moderate cases of RLS was 31.6% and for severe cases of RLS was 22.8% ($p=.005$).

Two month after treatment onset frequencies of mild, moderate and sever cases of RLS in group without substance abuse relapse were 62.8%, 20.5% and 14.1% respectively. In group with substance abuse relapse the frequency of mild, moderate and sever cases of RLS were 31.6%,34.6% and 25.7% respectively which showed significant difference correlation ($p = .0001$).

Three month after treatment onset frequencies of mild and sever cases of RLS in group without substance abuse relapse were 66.7% and 1.3% respectively while in group with substance abuse relapse the frequency of mild and sever cases of RLS were 22.8% and 19.9% respectively and there was significant difference statistically ($p = .0001$). (Table 2)

Table 2: Comparison of RLS severity at baseline, first, second and third month from withdrawal in the two groups

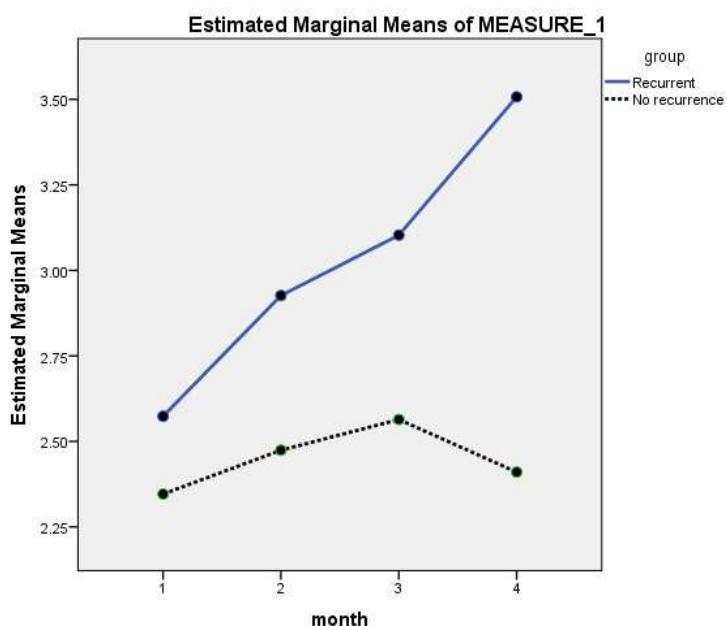
Groups		Without RLS No.(%)	Mild RLS No.(%)	Moderate RLS No.(%)	Sever RLS No.(%)	Very Sever RLS No.(%)	P-Value
Immediately After Withdrawal	patients with substance abuse relapse	9(11.5)	46(59)	12(15.4)	9(11.5)	2(2.6)	.39
	patients without substance abuse relapse	7(5.1)	76(55.9)	26(19.1)	22(16.2)	5(3.7)	
One Month After Withdrawal	patients with substance abuse relapse	4(5.1)	48(61.5)	13(16.7)	11(14.1)	2(2.6)	.005
	patients without substance abuse relapse	3(2.2)	51(37.5)	43(31.6)	31(22.8)	8(5.9)	
Two Month After Withdrawal	patients with substance abuse relapse	0(0)	49(62.8)	16(20.5)	11(14.1)	2(2.6)	.0001
	patients without substance abuse relapse	0(0)	43(31.6)	47(34.6)	35(25.7)	11(8.1)	
Three Month After Withdrawal	patients with substance abuse relapse	0(0)	52(66.7)	21(26.9)	4(5.1)	1(1.3)	.0001
	patients without substance abuse relapse	0(0)	31(22.8)	32(23.5)	46(33.8)	27(19.9)	

Repeated data test showed that there was a significant relationship among patients with substance abuse relapse and patients without substance abuse relapse regarding the severity of restless legs syndrome .(Table 3 and Figure 1)

Table 3. comparing the severity of restless legs syndrome in the two study groups

group	N	Mean	Std. Deviation	P value
Immediately After treatment	patients with substance abuse relapse	136	2.57	.948
	patients without substance abuse relapse	78	2.35	.923
One Month After treatment	patients with substance abuse relapse	136	2.93	.963
	patients without substance abuse relapse	78	2.47	.893
Two Month After treatment	patients with substance abuse relapse	136	3.10	.945
	patients without substance abuse relapse	78	2.56	.831
Three Month After treatment	patients with substance abuse relapse	136	3.51	1.054
	patients without substance abuse relapse	78	2.41	.653

*General Linear Model

**Figure 1.** comparing the severity of restless legs syndrome in the two study groups

Based on linear regression sex, education levels, family history of substance abuse and relapse have an effect on restless legs syndrome and its severity. (Table 4)

Table 4. Results of linear regression for factors affecting Restless Legs Syndrome

Factor	Impact Factor (β)	P-Value
Fixed Content	1.77	0.001
Sex	.877	0.001
Education Level	.517	0.001
Family History of Substance Abuse	.443	0.002
Substance Abuse Relapse	.164	0.001

DISCUSSION

This study was conducted to determine the relationship between restless leg syndrome and substance abuse relapse in patients with opioid dependency. The results showed that the frequency of RLS immediately after treatment in group without substance abuse relapse and in group with substance abuse relapse was almost similar. A case report study showed that three young adults dependent to opioids, had criteria for RLS including creeping/crawling/burning sensation in both the lower limbs especially at night when they lie down. Serum urea, creatinine, ferritin and thyroid function test were conducted for them which were normal. They were responded to ropinirole. Two of them improved within next 2 days and the third patient required dose escalation to 1.5 mg/day to show clinical improvement. This case report concluded that there might be an association between opioid dependency and RLS which requires further investigations[11]. In a study by Mahfoud et al, sleep disorders in substance abusers were investigated. The results showed that the prevalence of restless legs syndrome was very high (33%) compared to the general population (10%). The researchers concluded that drug abuse is a risk factor for restless leg syndrome[13]. A review article identified the relationship between RLS and taking medications. The study concluded that following drugs induced RLS: escitalopram; fluoxetine; L-dopa/carbidopa and pergolide; L-thyroxine; mianserin; mirtazapine; olanzapine; and tramadol[14].

The results of the present study showed that the severity of RLS in patients who had gone under substance abuse treatment and had substance abuse relapse was more than patients without substance abuse relapse and this trend increased by increasing the time from withdrawal, so that three months after treatment the frequency of mild and severe cases of RLS was high in group with substance abuse relapse than group without substance abuse relapse. Therefore it can be said that there is a relationship between opioid abuse and restless leg syndrome, and opium affects the severity of Restless Leg Syndrome. Perhaps the cause of RLS severity in group with substance abuse relapse with longer interval from treatment was more dependency to narcotics. Von Spiczak found a reverse correlation between opioid receptor numbers and severity of RLS symptoms in brain regions involved in the medial affective pain system. They interpreted that the more severe symptoms of RLS, the greater the endogenous release of opioids are in the medial affective pain system. The researchers hypothesized that opioids inhibit motor centers in the brain increase RLS severity[15].

In some studies opioids are considered as a new treatment for restless legs syndrome. In a study by Trenkwalder et al the efficacy and safety of a fixed-dose combination of prolonged release oxycodone–naloxone for patients with severe restless legs syndrome was investigated. The results showed that prolonged release oxycodone–naloxone was effective for short-term treatment of patients with severe restless legs syndrome[16]. In a meta-analysis by Hornyak et al, they performed comprehensive meta-analyses and indirect comparisons of RCTs for all currently recommended treatments of RLS. The results showed that besides the well-defined efficacy of dopaminergic treatment, other treatments including opioids have good efficacy with fewer side effects on RLS[17]. In a study by de Oliveira et al the effects of opioids compared to placebo treatment for restless legs syndrome in adults were evaluated. They concluded that Opioids are effective for treating RLS symptoms, but there are no reliable data regarding the important problem of safety[18]. Opioids are effective in the treatment of RLS symptoms and recommended for patients with severe symptoms of RLS, but they have side effects such as constipation, tolerance and dependency[18,19]. Crozer et al conducted a prospective study to determine whether the occurrence of postoperative RLS was associated with the type of anesthesia. They concluded that neither spinal anesthesia nor general anesthesia with propofol or an opioid induces or exacerbates the symptoms of RLS[20].

disfunction of the endogenous opioid, dopamine and iron systems are considered as pathogenesis of Restless Legs Syndrome (RLS). In a study by Sun et al they examined the interrelationship of these 3 systems in an in vitro model. The results of study showed that endogenous opioid system have a protective role on dopaminergic neurons. One of the mechanisms that have been proposed about the relationship between opioids and restless legs syndrome is opioids protective role on dopaminergic pathways of the basal ganglia of the brain[21].

There are some studies that suggest the use of opioids with caution for RLS treatment. In a retrospective study by Scherbaum, 120 opiate addicts who detoxified during a 5-month period were investigated. The results revealed that 15 of 120 patients showed the symptoms of transient RLS during opioid detoxification treatment[22]. Therefore opioids as monotherapy or add-on treatment for RLS should be considered when alternative satisfactory regimens are unavailable and the severity of symptoms warrants it[19]. Ghosh believed that RLS should be viewed as an independent disorder in opioid dependent patients because RLS response to dopamine antagonist proves that this syndrome is an independent disorder. Patients detoxified from opioids with persistent sleep disturbance should be screened for RLS before prolonging hypnotic prescriptions. The presumed etiological link between the two conditions and its management implications are discussed[11].

The linear regression of this study showed that sex, education level, family history of substance abuse and relapse are effective on Restless Legs Syndrome and its severity, so that in the third month from treatment (or detoxification) the chance of substance abuse relapse is increased.

CONCLUSION

The findings of this study showed a relationship between RLS and substance abuse relapse in opioid abusers who experienced substance abuse treatment, as the interval from treatment onset prolonged the severity of this syndrome increased.

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