

Research Article**Restless leg syndrome in amphetamine dependents undergone treatment in a longitudinal study****¹Gonabadi Nejad L, ²Ahmadkhanh HR,****³Moosavi Saadatabadi H and ⁴Fattah Moghaddam L**^{1,3}Department of Psychiatry, Iran University of medical sciences, Tehran, Iran²Iran university of Medical Sciences. Faculty of medicine. Mental health Research Center⁴Nursing Education, Lecturer, Department of Psychiatric Nursing,

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ABSTRACT

Objective: This descriptive-analytical study aimed to examine correlation between Restless leg syndromes (RLS) with amphetamine relapse. Methods: Case group included 170 amphetamine dependent abusers undergone treatment, which during treatment 100 of them (58/8%) experienced amphetamine abuse relapse and 70 of them (41/2%) did not. Control group included 190 persons without substance abuse. Results showed that severity of RLS during second month of treatment had the most important role in relapse of abuse which increases the risk of returning patient to substance abuse to 35/19 times more. (OR=35/19, CI=6/93-178/51, P-value=0/000). Severity of RLS in case group was mild at the beginning of the study then increased in first month of treatment and became severe in second month of treatment and again decreased in the third month, and finally the main reasons for amphetamine abuse relapse reported respectively: restless legs with 37 frequency (21/8%). In incidence frequency investigation of RLS in amphetamine abusers undergone treatment, 34 persons (43/9%) did not experience RLS which among them 23 persons (32/9%) did not have relapse of abuse and 11 persons (11%) experienced relapse. conclusion: amphetamine abuse withdrawal has affected severity of RLS, which was significant in the first month and recognized as an important factor in severity of syndrome.

Keywords: “Restless leg syndrome (RLS)”, “methamphetamine”**INTRODUCTION**

Substance abuse in almost all countries counts as a general health problem which is multifactorial and often has chronic and relapsing progression [1]. Recently due to more communications around the world, substance abuse pattern is changing and brand new substances like amphetamine are more accessible [2]. An important issue which should be considered in withdrawal of substance abuse and also relapse of abuse is the reason of withdrawal and relapse. Studies showed that about 80% of people came for withdrawal treatment experienced relapse in first six months and the cause of relapse classified in family, economic, social and personal factors [3]. In other words recognition and evaluation of causes and severity of effective factors of

substance abuse treatment and also relapse of abuse can be helpful in policy establishment and educational programs for substance abuse treatment [4].

Restless leg syndrome (RLS) is a common neuro-movemental disorder which almost is neglected [5, 6] and about 10% of adults suffer from that. One third of RLS patients have moderate to severe symptoms and need medical treatment [7]. Comparing to chronic disease such as Parkinson disease or stroke, this syndrome can decrease quality of life more significantly [8-11]. This syndrome affected sleep and mood [8, 10, and 11] and related to anxiety, depression [12-14] and low quality of life [13-16]. It also contains psychosocial impairment [17-18] and causes much social and

economical force for patients [8, 10-11]. Although its etiology is idiopathic[5], but many studies showed that deficiency in dopaminergic system is related to RLS[19-22] and also dopamine is one of the effective neurotransmitters in substance abuse pathophysiology(19). It can be hypothesized that there may be a correlation between amphetamine abuse and restless leg syndrome. So this study aimed to investigate RLS in amphetamine dependent patients comparing to those dependents with period of relapse.

METHODS AND MATERIALS

This descriptive-analytical study designed as a cohort study which performed longitudinal. Accessible sampling method was used and people with the terms of inclusion criteria entered to study respectively. Studying population contained amphetamine abusers who came for withdrawal treatment to an addiction clinic (Tehran Psychiatric Institute) and did not have relapse of abuse (first group) and patients who had relapse during treatment (second group).

Exclusion criteria included: 1) age under 18 years, 2) comorbid dependency to another substance, 3) false answers to questions by patient, 4) any peripheral nervous system disease such as diabetes, 5) consumption of psychiatric medication which can produce movemental disorders like akathisia, 6) consumption of any sedative or gaba stimulators which can cure RLS.

Each participant was informed about the goals and method of study and informed consent obtained from them. All participants filled demographic questionnaire included (age, gender, marital status, age of first substance abuse, other abused substances, withdrawal history, personal and familial psychiatric history) and RLS questionnaire at the beginning of study and 2 weeks after withdrawal treatment. Also a psychiatric interview performed to rule out BID, schizophrenia and any substance induced psychosis and GMC. Then RLS questionnaire refilled each month for 3 months and items like substance abuse due to

self-report, urine test for amphetamine abuse and quit of treatment were investigated.

Regarding these results patients divided in two groups: the ones who experienced amphetamine abuse relapse and those who did not. Frequency and outbreak ratio compared in two groups. Diagnosis criteria for RLS contained 1) tendency to move limbs with agitation and discomfort, 2) tendency to walk constantly or rubbing legs to each other to remove feeling of discomfort, 3) enhancement of symptoms at the time of rest and recover by activity permanently, 4) enhancement of symptoms in early day or night[23].

Expectation items included: 1) if patient had RLS before and cured spontaneously or is under treatment with specific drug and experience symptoms alternatively, 2) patients who earlier recovered by activity, but recently do not and have severe symptoms, 3) patients who earlier only had symptoms at day or night but recently became equal in day and night. Regarding clinical history, patients with RLS distinguished from those who were not. Then by using 10 items questionnaire severity of RLS determined. Scores counted from 0 to 40 as Score 0: no sign of RLS, 1 to 10: mild, 11 to 20: moderate, 21 to 30: severe and 31 to 40: very severe. Statistical tests used in this study included t-test to compare quantitative variables, Mann-Whitney U test to compare ranking variables and chi-square used to compare proportions. Statistical significance limitation in this study was 0.05 and SPSS-20 was applied.

Findings

In this study, two case groups included 170 amphetamine dependents undergone treatment, that 100's of them (58/8%) experience relapse during treatment and 70 persons (41/2%) did not. Control group included 190 persons with no history of substance abuse which randomly chosen from gynecology, dermatology and urology clinics and evaluated only by age, gender and RLS. It should be noted that total number of participants in case group was 190 which 20 of them, 13 men (65%) and 7 women (35%) with average age of 24/10₋₄/62 and 12 (60%) frequency of moderate RLS were

not entered to study because relapse of abuse and RLS during first, second and third month did not recorded.

However, in evaluating of control group at the beginning of study 160 persons (84/2%) did not have RLS and the most frequency of RLS belonged to 19 persons (10%) with mild RLS. In case group the most frequent mild RLS was 65 persons (38/2%) and 45 persons (26/5/5) with moderate RLS. Severity of RLS almost was mild in two groups at the time beginning the study but increased during first and second month of treatment and again decreased in third month.

Finally the main reason for relapse of abuse was restless legs with 37 frequencies (21%) and irritability with 25 frequencies (14/7%). In incidence frequency of RLS investigation of amphetamine abusers undergone treatment at the beginning of study, 34 ones (43/9%) did not have RLS which among them 23 ones (32/9%) did not experience relapse and 11 ones (11%) had the period of relapse; also in patients with relapse, severity of RLS as moderate, severe and very severe (intense) reported more than ones who had not relapse, in the other hand in control group with no history of substance abuse 160 ones (84/2%) did not have RLS and the remained ones had mild RLS. So using qui-square test it can be said that there was a significant difference among incidence frequency distribution of RLS in 3 groups. (p-

value<0/05). Control group had no evaluation of syndrome severity during 3 months due to no history of substance abuse and only the rate of incidence recorded for them (1/23+_0/60). So incidence frequency of distribution of RLS in undergone treatment patients was determined and compared:

Table 1 shows incidence frequency distribution of RLS during first, second and third month of treatment in patients with period of relapse or without, separately. According to this table patients without relapse had decreasing rate of RLS severity during time, but patients with relapse showed increasing rate comparing to the entrance time to study which enhanced at first month and more in second month and finally decreased in third month and they started recovery process and rate of outbreak and severity among them decreased that these differences were statistically significant using qui-square test (p-value<0/.05).

Evaluation of severity rate of RLS among two groups of amphetamine abuse relapse and without relapse compare by using independent t-test and still there was significant difference between two groups. Chart 1 shows trend of average of severity of RLS during time, as it is showed in the charts patients with relapse periods reported more average of severity of syndrome and also enhancement of severity during time which finally decreased at the third month of treatment.

Table1: logistic regression results for RLS standardized coefficients (β) on relapse of methamphetamine dependents

P-Value	CI (95%)	OR	(β)	
0.806	0.45-2.75	1.119	0.12	RLS Primary RLS
0.001	0.03-0.40	0.114	2.16	RLS RLS in first month
0.000	6.93-178.51	35.19	3.56	RLS RLS in second month
0.023	1.20-12.16	3.82	1.34	RLS RLS in third month

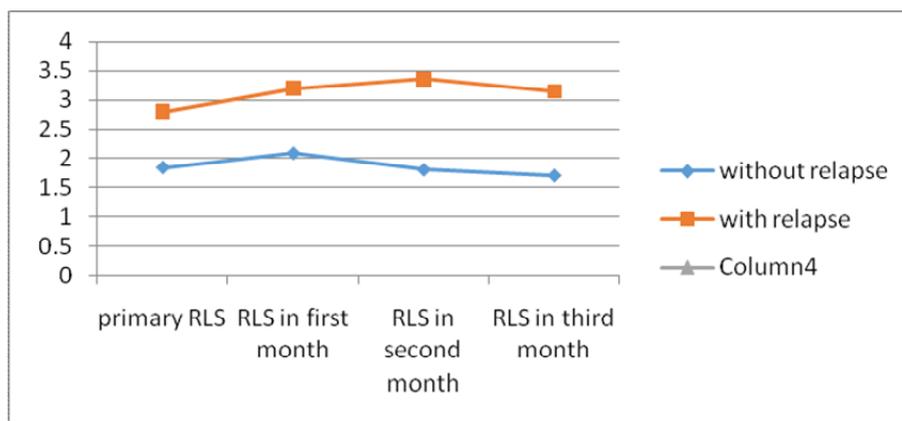


Chart 1: linear chart for average severity of primary and 3 months RLS during treatment

Table 2 shows the results of logistic regression for the effect of RLS severity on amphetamine dependents undergone treatment, according to this table, primary RLS cannot be an important factor for relapse, but RLS during months of treatment can be an effective factor in relapse as it is increased risk of relapse in first month to 0/114 and the most effect of syndrome

severity which increased risk of relapse 35/190 times more reported in second month. After discussion about frequency distribution of RLS among amphetamine dependents and control group, it is necessary to investigate relationship of factors effective on RLS incidence in patient who undergone treatment:

Table 2: comparison of RLS incidence frequency during first, second and third month of treatment

P-Value	RLS incidence in first month:				Without syndrome	Case group
	intense	sever	moderate	mild		
P<0/001	(0%)0	(2.9 %) 2	(22.9%)16	(54.3%)38	14(20%)	Without relapse
	13(13%)	(28%)28	28(%28)	27(%27)	4(%4)	With relapse
P-Value	RLS incidence in second month:				Without syndrome	Case group
	intense	sever	moderate	mild		
P<0/001	(0%)0	(0%)0	7(10%)	42(60)	21(30%)	Without relapse
	12(12%)	31(31%)	38(38%)	18(18%)	1(1%)	With relapse
P-Value	RLS incidence in third month				Without syndrome	Case group
	intense	sever	moderate	mild		
P<0/001	(0%)0	(0%)0	2(2.9%)	45(46.3%)	23(32.9%)	Without relapse
	5(5%)	31(31%)	43(43%)	15(15%)	6(6%)	With relapse

Table 3 showed results of RLS incidence and frequency in amphetamine dependents with or without relapse during time by gender; as it is obvious in the table men with relapse had more frequency distribution of RLS than women with relapse, in other words men with relapse showed most primary RLS frequency with moderate severity,(31 ones,39/7%) and women with relapse had frequency of 8 persons(36/4%) with mild severity, which can be said that severity of this syndrome was more in men than women; also in control group primarily severity was more in men comparing to women as

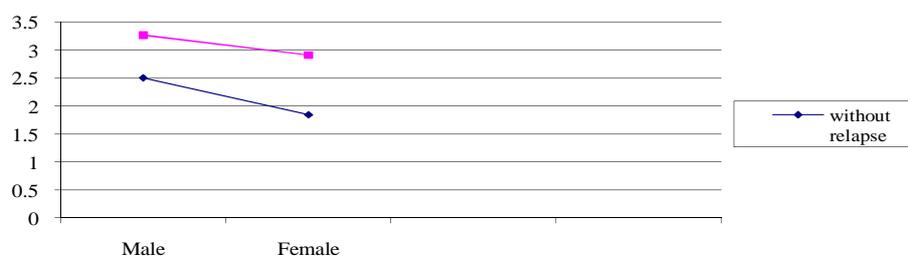
almost women did not have sever primary RLS and these differences considered significant statistically using qui-square(p-value<0/05). According to table 3 and chart 2 RLS severity investigation by gender in the two groups of with relapse and without relapse, showed syndrome frequency and severity higher in patients with relapse and female gender showed lower incidence and severity of syndrome, also as time passed by severity of RLS increased during first and second month, but decreased in third month, although there was difference in incidence and severity of syndrome in the

groups with relapse and without relapse by gender, but using qui-square showed no meaningful difference in RLS incidence by gender in patients with relapse(p-value>0/05), in patients without relapse also primary RLS

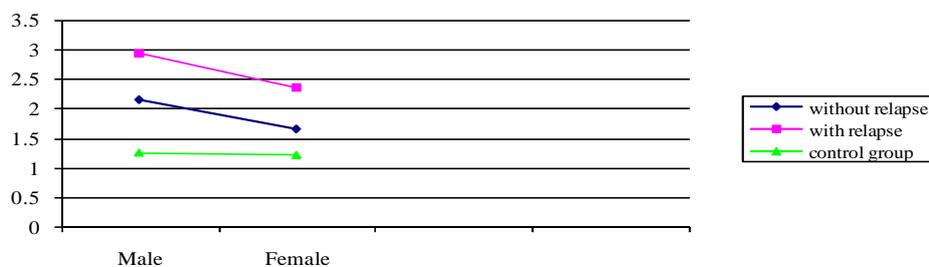
incidence and severity was more than female gender which was statistically significant(p-value<0/05).

Table 3: gender based comparison of incidence frequency distribution of primary RLS, and 3 months of treatment

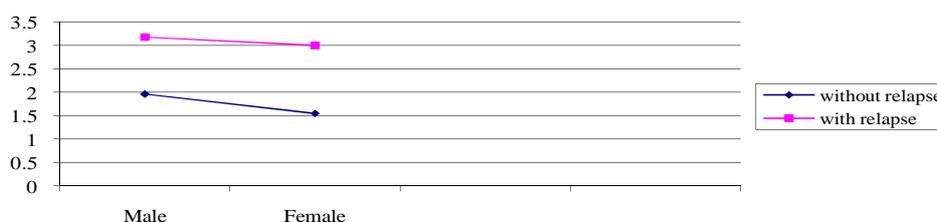
	P-Value	df	χ^2	gender based syndrome incidence
0.134	3	5.58	Control group	incidence RLS in primary month gender
0.020	3	9.85	Without relapse	
0.178	4	6.29	With relapse	
0.001	3	17.63	Without relapse	incidence in first month gender
0.473	4	3.53	With relapse	
0.012	2	5.81	Without relapse	incidence RLS in secondary month gender
0.734	4	2.01	With relapse	
0.003	2	11.87	Without relapse	incidence RLS in third month gender
0.837	4	1.44	With relapse	



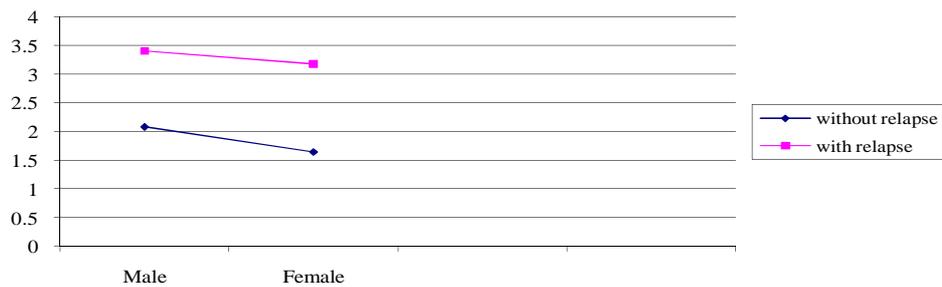
Primary RLS



RLS in first month



RLS in second month



RLS in third month

Chart 2: linear chart of gender based average severity of primary syndrome and 3 months treatment in case and control group

From now on, effective factors on RLS severity without considering relapse evaluated in all patients undergone treatment. Results from linear regression in order to investigate effective factors on RLS declared in table 4. Factors evaluated in this study included gender, reason of relapse, marital status, education level, substance abuse relapse, age of first substance abuse, withdrawal history, family history of substance abuse, smoking cigarettes and times of substance abuse, but in table 4 only the factors effective on RLS incidence and severity was shown. As it is shown gender, age and reason of relapse affected primary RLS before treatment; in the first month of treatment

gender, age, reason of relapse and relapse of abuse affected severity of RLS and as it is obvious in table substance abuse withdrawal affected RLS severity especially in the first month which was considered statistically effective on syndrome severity. Severity of syndrome in second and third month of treatment only related to gender and reason of relapse, it can be said that the first month of treatment was the most effective period on severity of syndrome and patients had more tendency to substance abuse again during this month.

Table 4: factors effective on incidence and severity of RLS

P-Value	(β)	factor	
0/001	0.446	gender	
P<0/001	0.039	age	Primary RLS
P<0/001	0.250	reason of relapse	
P<0/001	0.497	Gender	
P<0/001	0.016	age	RLS in first month
P<0/001	0.712	substance abuse relapse	
P<0/001	0.405	reason of relapse	
0/004	0.325	gender	RLS in second month
P<0/001	0.344	reason of relapse	
0/008	0.301	gender	RLS in third month
P<0/001	0.317	reason of relapse	

DISCUSSION AND CONCLUSION

The purpose of research was to investigate effect of restless leg syndrome in rate of relapse in amphetamine abusers in a longitudinal study. At the time of entrance to study in case group (amphetamine dependents undergone treatment) RLS incidence reported mild with 65 persons frequency (38/2%) and moderate with 45 persons frequency (26/5%) and in control group the most frequent RLS was mild with frequency of 19 persons (10%). Also severity of RLS in case group at the time of entrance to was almost mild which was increased during first and second of treatment and decreased during the third month and finally the main reason for relapse of abuse reported rest legs with the frequency of 37 ones (21/8%), anger and irritability with the frequency of 25 ones (14/7%).

Results of present study about frequency of RLS syndrome incidence in amphetamine abusers at the beginning of the study showed that 34 persons (43/9%) did not have the syndrome and 11 ones (11%) among them reported relapse. Rate of RLS severity as moderate, sever and intense was higher in patients with period of relapse comparing to those who had not relapse, also control group of this study which had no history of substance abuse, just reported primary RLS(with severity of $1/23 \pm 0/60$), so severity of syndrome during 3 months was not evaluated. Accordingly it can be suggested that RLS had an important role in relapse of substance abuse, as in control group with no history of substance abuse, 160 ones(84/2%) did not have primary RLS and the remained ones only experienced mild RLS.

Methamphetamine abuse can cause permanent cognitive disorders and central nervous system deficiency which can lead to more rate of substance abuse and relapse. This deficiency in nervous cells may lead to prefrontal cortex (PFC) and Systems. Studies suggested that neuron changes induced by amphetamine abuse can be considered as a factor to relapse of abuse [24] Dopamine enhancement can lead to impulse control disorders and dopaminergic system dysfunction exists in people with these

disorders such as gambling and substance abuse [25-26].

Results of present study showed that severity of RLS in the group with relapse was higher than the group without relapse. Linear regression results in order to evaluate effective factors on RLS severity showed that gender, age and the reason of relapse affected primary RLS severity; in the first month after treatment, factors as gender, age, reason of relapse and the relapse itself affected RLS severity, so it can be concluded that substance abuse withdrawal affected severity of RLS which was significant in the first month and considered as an effective factor statistically.

Severity of syndrome in second and third months of treatment depended on factors like gender and reason of relapse, in other words it can be said that first month of during treatment is the most important one on RLS severity and due to probable disorders during this month can cause more tendency in patients to return to substance abuse.

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