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Research Article

Efficacy of Regulated 12-Session Matrix Model on restraining methamphetamine-dependence: Biological evidence and self-reports

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ABSTRACT

Introduction: Substance abuse is accompanied by a wide range of psychological, social, and economic adverse outcomes and damages. Methamphetamine (ab)use is dangerous because of its wide range adverse outcomes and hazardous sustaining side effects. Moreover, Methamphetamine-dependence is usually treatment-resistant. This study evaluated the *Regulated 12-Session Matrix Model* in treatment of outpatient methamphetamine-dependent individuals.

Method: 24 individuals were chosen according to inclusion/exclusion criteria of the study and randomly assigned to equal experimental (age range 19-41; mean age: 46.9) and control groups (age range: 21-42; mean age: 27.8). Experimental group members partook *Regulated 12-Session Matrix Model* once a week in 12 consecutive weeks, while control group members remained at waitlist.

Results: Independent t-test in 12th week showed that experimental group had lower methamphetamine use, comparing to control group ($p<.05$).Phillai's Trace, Wilk'sLambda,Hotelling-Lawley's trace, and Roy's largest root showed that there are significant association between experimental and control groups in reduction of methamphetamine-use lapse ($p<.05$).Within-subject F ratio revealed that "methamphetamine use" was significantly reduced in experimental group after clinical intervention ($p<.001$). Urine test showed significant difference in results of negative responses by the end of intervention ($p<.05$) in experimental group, compared to control group, which was also significant from the results of both groups in pre-test ($p<.001$).

Discussion and conclusion: Efficacy of *Regulated 12-Session Matrix Model* in craving control and reduction of lapse and substance (ab)use in methamphetamine-dependent patients was approved with self-reports and biological indicators. *Regulated 12-Session Matrix Model* has been proved to be beneficial in methamphetamine-dependencetreatment in Iran and other alike cultural and social atmospheres. Limitations and future implications are discussed.

Keywords: Regulated 12-Session Matrix Model, Methamphetamine, substance use disorders (SUD), relapse, substance abuse, craving, lapse, urine test, susceptibility.

1. INTRODUCTION

Substance use disorders (SUDs) are usually accompanied by mental disorders and this comorbidity is to the extent that in recent years many of psychiatric and pharmaceutical studies are focused to explore such relation. Increasing evidence suggest that SUDs are higher in clinical

population than non-clinical society sectors (1, 2). This comorbidity has resulted in an augmentation in disability due to illness all around the world (3, 4). One of the reasons of explaining such comorbidity is that psychological disorders have mutual and reciprocal impact on each other, so that as an example, high levels of alcohol use in alcohol-dependent individuals would cause major depressive disorder (MDD) among them (5, 6). Sometimes people with psychological difficulties resort self-therapy and willfully use drugs/substances. The third likelihood may because of common reasons such as genetic predisposition, and/or socioeconomic factors (e.g., poverty, harm, and/or learned behaviors/actions within the family) which simultaneously result in psychological disorders and SUDs (6, 7). In addition, increasing availability of access to drug/substance in recent years, is considered as another factor of increment of SUDs in societies all around the world. The important issue is that SUD in any type is a high-risk ground of vast personal and interpersonal problems in the community which could not be easily ignored (8).

Nowadays, SUD become a major risk in psychological and social debates. Substance abuse is accompanied by a wide range of psychological, social, and economic adverse outcomes and damages include co-occurring of psychological disorders like attention deficit/hyperactivity spectrum disorders (ADHD), conduct disorder, antisocial personality disorder (APD), affective disorders, anxiety disorders, problematic and high-risk sexual behaviors, educational, familial, and occupational difficulties, school/university dismissal, delinquent behaviors, driving accidents and incidents, high-risk behaviors, suicide, and self-mutilative behaviors (9-15).

The most popular stimulant substances are methamphetamines, which are known as *Shishé* in Iran. Global reports indicate increasing use of methamphetamine among people, especially youth, so that after cannabis the second world rank of substance use is for methamphetamine (16). Unfortunately, methamphetamine use become a cultural mainstream especially among adolescents and young adults (17, 18), and the same is in Iran (19). Between 2010 and 2011, the rate of ask and use of methamphetamine raised 400%; compared to 238% rise in Mexico, 166% in Thailand, 153% in USA, and 140% in China, Iran gained the global first rank of increase in ask and use of methamphetamine which has made all country and global responsible institutions deeply concerned. The rate of methamphetamine use in Iran is reported between 6-20% in various population sectors (15, 19, 20). Because of high amount of ask and use of methamphetamine drugs and their huge damages especially on central nervous system (CNS), International institutions of SUD research have announced this group as research priority in substance use in Asian countries and societies (21).

Using various substances according to psychiatric criteria would lead to the diagnosis of SUD. These include alcohol, cannabinoids, hallucinogens, inhalants, opioids, sedatives, anxiolytics, soporifics, dissociative anesthetics, stimulants, and even tobacco. In DSM-5 substance use is different from substance abuse, and substance dependence, and each of them have distinctive classifications. In DSM-5 diagnosis of SUD is used whenever individual has at least two of the listed symptoms in past 12 months. Then, intensity of disorder would be determined in one of three modes of mild (2-3 symptoms are present), moderate (4-5 symptoms are present), and severe (6 and/or more symptoms are present). The first domain of diagnosis is the loss of control behaviors, such as frequent over-use of drug/substance. Social problems due to substance abuse are in the second domain including constant interpersonal problems which are produced or intensified by substance/drug. The third domain comprises high-risk behaviors like continuing substance

abuse despite frequent physical and/or psychological problems. The final domain is related to physiological changes which are the result of substance use and consist of issues include the need to higher dose of substance use to reach the same previously-experienced results, craving, lapse, withdrawal, and tolerance (22).

Amphetamine-type stimulant substances result in dangerous, unwanted, and hazardous outcomes in users. Methamphetamine has a wide range of damaging and debilitating side effects which comprise serious problems in behavioral inhibition and self-control, increase of impulsivity, increase of delay discounting, high increase in risk of Parkinson' disease morbidity, memory decline, increase of mRNA levels of brain-derived neurotrophic factor (BDNF) in prefrontal cortices and amygdala and reduction in the protein levels of BDNF in hippocampus (23-26). Methamphetamine has devastating effects on brain structures, because of inversion of the flow of vesicular neurotransmitters and dopamine transmitters simultaneously. In such situation, methamphetamine acts as dopamine releaser and cause a severe dopamine toxicity in CNS (27). The most complex issue in methamphetamine abuse is its craving, because various neuro-circuits of reward and motivation are activated during the phase of craving. These neuro-circuits comprisethe nucleus accumbens, dorsal striatum, orbitofrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex (DLPFC), amygdala,hippocampus and insula(28, 29).

One of the newly established methods of methamphetamine-dependence treatment is Matrix Model for condense and outpatient treatment of patients. Matrix Model is composed of a set of complementary therapeutic strategies which are mixed together to make an integrated therapeutic experience for outpatient patients. Matrix Model is a set of evidence-based medicine (EBM) methods which is designed as a program for people with SUD. This model is based on clinical studies in the domains of behavioral therapy, relapse prevention research, motivational interview strategies, psycho-education information, and partaking in 12-steps programs (30-32). Matrix model has been administered in varied studies to treat methamphetamine dependence and reducing craving and lapse (33, 34). The original matrix model is based on a 24- to 36-session process of intervention which has its own cons which has been explained previously and authors have tried to modulate and reformulate the criteria and process of matrix model, so that it could be applicable in 12 sessions (35).

Several studies has been conducted to evaluate the application and feasibility of matrix model on treatment of methamphetamine dependence (33, 36-39). However, there are just a few studies on the efficacy of matrix model on treatment of craving, and lapse in the therapeutic process of methamphetamine-dependence withdrawal (40-43). According to such issues authors have conducted a series of quasi-experimental clinical trials determine the efficacy of regulated 12-session matrix model on reduction of susceptibility, lapse frequencies and use of methamphetamine in methamphetamine-dependent patients. The previous study (35) was based upon the repeated consecutive weekly measurement of methamphetamine use by methamphetamine-dependent patients. The results were hopeful to substitute the 12-session regulated matrix model on treatment of methamphetamine-dependence. The present study is a further investigation by weekly urine test in order to empower the evidence by physiological findings.

2. METHOD

2.1. Design

In order to conduct the study, randomized clinical trial which based on quasi-experimental design with repeated measures, was implemented. Because of the experiment accuracy and the facilities of study environment, the study was

conducted in *Tehran Addiction Withdrawal Center*, Tehran, Iran in the year 2012.

2.2. Participants

In this study, after screening according to inclusion and exclusion criteria of study, 24 individuals, from those who referred to a SUD treatment center, Tehran, Iran in the year 2012, were chosen and randomly assigned to equal experimental (age range 19-41; mean age: 46.9) and control groups (age range: 21-42; mean age: 27.8).

The study had both inclusion and exclusion criteria in order to increase the precision of assessments.

The inclusion criteria comprised methamphetamine dependence according to DSM-IV-TR (44), having the motive to withdraw (coming to SUD treatment center and asking for help to withdraw), confirmation of administration of all procedures of the therapeutic intervention (participation in all 12 sessions once a week for experimental group members, acceptance to remain in waitlist in the time of administration of the intervention for control group members). In addition, the exclusion criteria consisted of having history of past and/or present major psychiatric disorder such as psychosis, major depressive disorder (MDD), severe anxiety disorder, SUD other than methamphetamine, cognitive developmental disorder (IQ 30 points below society's average), severe physical and/or cognitive disorder which intervene the therapeutic phase, and using drugs such as methadone or naltrexone.

2.3. Intervention

The process of intervention comprised 12 sessions of mixed varied CBT techniques aimed on craving management and control in 12 once-a-week consecutive sessions (*Regulated 12-Session Matrix Model*).

The design of the study was quasi-experimental with repeated measures in which the therapeutic outcomes of *Regulated 12-Session Matrix Model* are evaluated through all the procedure. All the participants of experimental group undergone *Regulated 12-Session Matrix Model* once a week (Table 1). Inclusion criteria were administration method methamphetamine use (smoking), and having no history of past or present severe psychotic, depressive, and/or anxious signs/symptoms which need treatment.

Table 1. sessions of *Regulated 12-Session Matrix Model*

Session	Topic
1	Why I withdraw substance? (Justice balance)
2	Starters and their types
3	Major problems in remission: Family mistrust/ Enegry reduction/ Drug misuse
4	Lapse and ways of coping with it
5	Thoughts, feelings, and precedent behaviors
6	Impatience and depression
7-8	Preventive and susceptible activities to relapse/ sexual relations
9	Occupation and remission/ getting involved
10	Shame and guilt/ Honesty
11	Motive to remission/ full abstinence
12	Anticipation of relapse

Follow-up indices (dependent variable) included weekly use of methamphetamine in gram as well as urine test twice a week.

4.2. Instruments

1.Primary screening from comprised inclusion/exclusion criteria of the study.

2.DSM-IV-TR criteria for diagnosis of SUD/methamphetamine dependence(44).

3.Patients' information registration form, which include, patients code, age, gender, marital status, educations, wages, history of methamphetamine use, daily usage dose of methamphetamine (gram/day), administration type, etc.

4. Follow-up form, in which (non)occurrence of lapses, amount of methamphetamine use (number of times of use during last week and dose of usage (gram/day) in each time) were registered.

5. Self-report form, in which daily use of methamphetamine were reported twice a week by participants after administration of urine test.

6.Urine test Kit, by which methamphetamine administration in participants were tested twice a week. This kit can trace methamphetamine use in last 48 hours.

2.5. Data analysis

according to the study design, in addition to descriptive indices, T-test for independent groups, multivariate tests of Phillai's Trace, Wilk's Lambda, Hotelling-Lawley's trace, and Roy's largest root as well as analysis of variance were administered.

2.6. Ethics

Prior to initiation of the intervention phase, the procedure was completely explained to all participants, and then, they have filled out written consent in which the general trend and aims of the study was discussed. In order to meet the criteria of confidentiality, identity of all participants were kept secret and the individual evaluations and results of participants were restricted from access. Considering research and medical ethics in the study and avoiding deprivation of methamphetamine dependent patients from *Regulated 12-Session Matrix Model*, all the control group participants have undergone the therapeutic plan after the intervention phase accomplished.

3. RESULTS

3.1. Methamphetamine use

Data of the step-by-step gradual assessments of methamphetamine use in both experimental and control groups are presented in table 2. According to table 2, the highest methamphetamine use in experimental group was in first week, at initial session (mean: 2.04 grams/day), while the highest methamphetamine use in control group was in second week (mean: 2.01 grams/day). Independent t-test calculation for first week shows no significant differences between experimental and control groups. However, independent t-test in 12th week showed that experimental group on which *Regulated 12-Session Matrix Model* was administered, had lower methamphetamine use, comparing to control group ($p<.05$).

Table 2: Statistical indices of methamphetamine use (gram/day) during study

Step	Group	Central tendency indices			Variance indices			Distribution indices		
		Mode	Median	Mean	Range	variance	SD	SEM	Skewness	Skewness coefficient
Screening	Experiment	1.50	1.50	2.04	7	6.61	2.57	.74	.30	.65
	Control	3.50	2	2	3.50	2.17	1.47	.42	-.14	-.90
Week 1	Experiment	1.29	1.29	1.29	7	6.47	2.54	.73	.80	.90
	Control	3.50	2/25	.40	3.50	1.96	1.40	.40	-.43	-.49
Week 2	Experiment	.85	.85	.85	7	4.47	2.11	.61	.71	.35
	Control	3	2.50	2.01	3.50	2.01	1.42	.41	-.36	-.73
Week 3	Experiment	.62	.62	.62	3.50	1.46	1.20	.34	.78	.07
	Control	2	2	1.68	3.50	2.32	1.52	.43	-.10	-.05
Week 4	Experiment	.50	.50	.50	3.50	1.40	1.18	.34	.20	.71
	Control	2	2	1.65	3.50	2.02	1.42	.41	.01	-.79
Week 5	Experiment	.33	.33	.33	3.50	1.01	1.01	.29	.34	.36
	Control	1.35	1.35	1.40	3.50	2.11	1.45	.41	.12	-.14
Week 6	Experiment	.34	.34	.34	2.10	.50	.70	.20	.04	.18
	Control	.66	.66	.66	3.50	1.18	1.09	.31	.94	.64
Week 7	Experiment	.26	.26	.26	2.10	.37	.61	.17	.82	.44
	Control	.10	.10	.45	2.50	.55	.74	.21	.23	.27

Week 8	Experiment	.020	.020	.020	2.10	.36	.60	.17	.26	.88
	Control	.95	.95	1.09	3.50	1.33	1.15	.33	.71	-.27
Week 9	Experiment	.17	.17	.17	2.10	.36	.60	.17	.46	.01
	Control	.43	.43	.43	3.50	1.01	1.01	.29	.03	.54
Week 10	Experiment	.12	.12	.12	1.50	.18	.43	.12	.46	.01
	Control	.54	.54	.54	3.50	1.24	1.11	.32	.16	.25
Week 11	Experiment	.07	.07	.07	.90	.06	.25	.07	.46	.01
	Control	.29	.29	.29	2	.32	.57	.16	.78	.38
Week 12	Experiment	.07	.07	.07	.90	.06	.25	.07	.46	.01
	Control	2	2	1.41	3	1.33	1.15	.33	-.20	-.86

Independent t-test			
	Independent t	df	α
First week	.04	22	.962
12th week	11.61	22	.001

Using four multivariate tests of Phillai's Trace, Wilk's Lambda, Hotelling-Lawley's trace, and Roy's largest root showed that there are significant association between experimental and control groups in reduction of methamphetamine-use lapse ($p<.05$). *Regulated 12-Session Matrix Model* with emphasis on "craving management and control skill" reduced amount of methamphetamine use (in experimental group) more than just the regular assessment of methamphetamine use (in control group; Table 3).

Table 3: Multivariatetests to evaluate associations between dependent variables of levels of methamphetamine-use lapse

	Multivariate test	**F ratio**	**df**
Index	Philla's Trace	3.56	.045
	Wilk's Lambda	3.56	.045
	Hotelling's Trace	3.56	.045
	Roy's Largest Root	3.56	.045

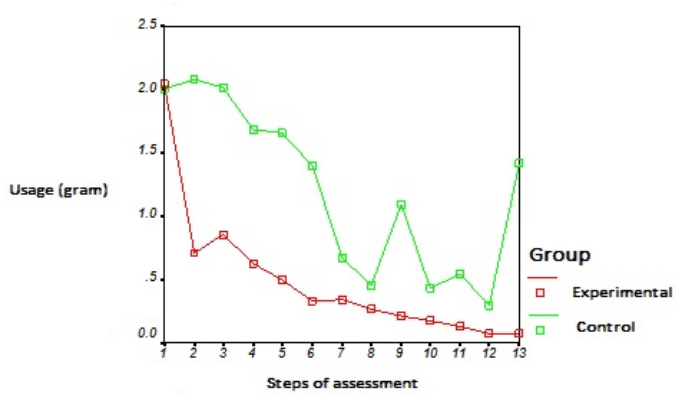
Change in groups were investigated in two levels of within- and inter-subject via analysis of variance. Within-subject F ratio calculation for different assessment levels with emphasis on administration of "craving management and control skills" revealed that there are significant differences in 13 levels of assessment of "methamphetamine use" in experimental group ($p<.001$). The highest usage amount in experimental group was in initial session (mean: 2.04 grams/day) and the usage amount decreased gradually from session one to twelve. Therefore, "craving management and control skills" training was efficient and reduced lapses in methamphetamine-dependent individuals (effect size: .28). In addition, F ratio test administration in experimental group was significant ($p<.05$; table 4).

T

able 4: F test to investigate the significance of *Regulated 12-Session Matrix Model* in methamphetamine-use craving reduction

		Sum of squares	**df**	**Mean of squares**	**F ratio**	**α**	**Effect size**
Within subjects	Index	85.66	5.89	14.52	8/72	.001	.28
	Error	216.02	129.75	1.66			
Inter subjects	Index	40.56	1	40.56	4.33	.049	.16
	Error	206.07	22	9.36			

Graph 1 illustrates the effect size of *Regulated 12-Session Matrix Model* in reduction of methamphetamine-use craving in both experimental and control groups within 13 sessions of assessment, based on self-reports of usage (gram/day).



Graph 1: Trend of methamphetamine-use craving reduction in the process of *Regulated 12-Session Matrix Model*.

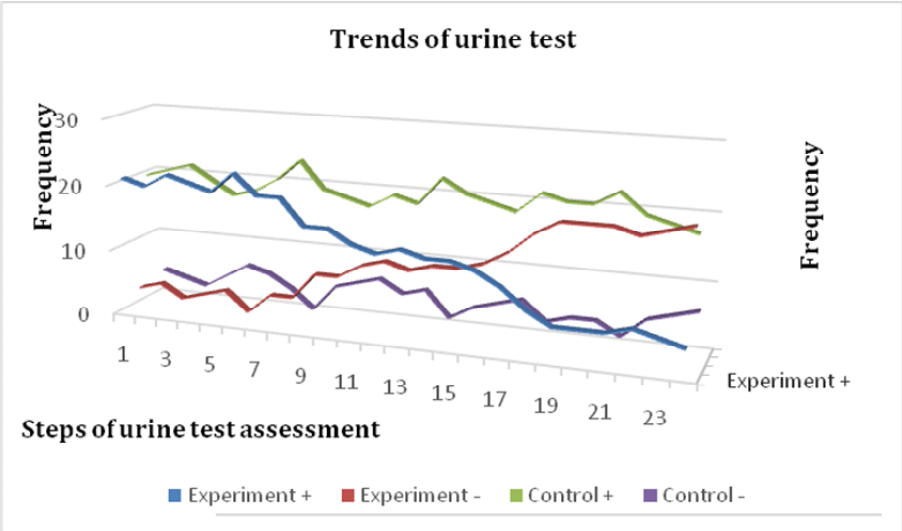
3.2. Urine test

In order to assess the efficacy of treatment urine test was administered twice a week on participants. Table 5 shows the urine-test results of participants at the first day of initiation of *Regulated 12-Session Matrix Model*. These results indicate that 87.5% and 83.33% of experiment and group members, respectively, had positive results in urine test by the start of the therapeutic program. The chi-square results of comparing two groups of experiment and control shoed no significance difference among them. In contrast, the last urine-test results by the end of the intervention at week 12 revealed that 16.66% of experiment group members had positive results in urine test, comparing to 75% positive results among control group members. Chi-square results of post-test between two study groups were significant ($p<0.05$). The Chi-square test between experiment and control groups in positive and negative results of urine test showed significant differences in both negative and positive responses just in experimental group ($p<.001$).

Table 5: Results of urine test

		Experiment		Control		Total	
	Urine test result	Frequency	Percent	Frequency	Percent	Frequency	Percent
Pre-test	**Positive**	21	87.5	20	83.33	41	85.41
	Negative	3	12.5	4	16.66	7	14.58
Chi-Square	Ratio: 1.59	Df: 1		Sig: .125		Concordance coefficient: .20	
Post-test	**Positive**	4	16.66	18	75	22	45.8
	Negative	20	83.33	6	25	26	54.16
Chi-Square	Ratio: 3.58	Df: 1		Sig: .048		Concordance coefficient: .36	
Chi-Square	Experiment Positive: 5.08 Df: 1 Sig: .001			Control Positive: 1.03 Df: 1Sig: .917			
	Experiment Negative: 6.37 Df: 1 Sig: .001			Control Negative: .98 Df: 1Sig: .859			

The trends of urine test results in both experiment and control groups are illustrated in graph 2 which demonstrates the effect size of *Regulated 12-Session Matrix Model* in reduction of methamphetamine-use within 12 weeks of assessment.



Graph 2: Trends of urine test results in the process of intervention

4. DISCUSSION AND CONCLUSION

Evidence-based practices (EBP) and scientifically controlled studies has shown no efficacy of pharmacotherapy on reduction of methamphetamine craving in users yet, and still the best and preferred intervention is psychotherapy (10, 19, 20). Therefore, in order to achieve more therapeutic outcomes, authors ought to modulate the psychotherapies and make them sub-culturally specific to their patients/clients, so that the new therapeutic modulations fit to their patients/clients and meet their special needs. In doing so, authors have tried to adapt matrix model of SUD treatment to methamphetamine-dependent patients in Iran. This resulted in formation of *Regulated 12-Session Matrix Model* which is both cost-effective and beneficial in reduction of methamphetamine-use craving and laps in patients (35).

Methamphetamine use and craving was gradually reduced throughout implementation of *Regulated 12-Session Matrix Model* in experimental group, which has been statistically approved by measuring methamphetamine usage reports and urine tests. Outcomes of the study indicate utility of *Regulated 12-Session Matrix Model* in treatment of methamphetamine dependence. Findings of the present study are in line with previous studies in the domain of implementation of CBT in SUD treatments, especially on craving control.

In line with previous studies, SUD treatment centers which offer modern therapies and therapeutic approaches, in addition to increase the coming sessions of varied patients during the time, would retain patients more in therapeutic process and therefore, have more efficacy on reducing SUD in the society (35, 45). In a recent study in USA, 600 SUD patients were undergone various psychotherapies. Results revealed that psychotherapy, especially when modified and regulated with each individual and her/his SUD, and implementing CBT methods along with 12-step paradigm, are most effective in reduction of craving and substance use (46).

Most of the studies about SUD treatment emphasize on the importance of therapeutic process on the therapeutic results. In a study on veterans with SUD, it has been revealed that issues such as impulsivity, low self-efficacy, unplannedness, and having poor coping strategies would result in inability to follow therapeutic process of SUD. Furthermore, Helping patients in planning therapeutic process and collaboration of therapists with them in therapeutic plans, especially paying attention to the way of expressing impulsivity [important indices of

Regulated 12-Session Matrix Model], can significantly improve therapeutic outcomes (47).

Studies on craving management and lapse reduction in people with SUD showed that psychotherapies which reinforce processes such as acceptance, awareness, and non-judgment in SUD patients can significantly reduce substance use craving, and prolong abstinence periods as well as stability of treatment (48). It appears that *Regulated 12-Session Matrix Model*, which is an evolved and enriched version of 12-step method, would have the potential of becoming an effective method of treatment in the domain of SUDs.

Matrix Model has notable efficacy in treatment of SUDs, especially methamphetamine dependence, so that longitudinal studies has proven enhancement of ability to abstinence, resistance to lapse, and management and reducing craving in patients whom undergone this model (30, 33, 34, 38, 49). The underlying logic of Matrix model in treatment is implementing a set of preventive methods to reduce the craving and lapse in people with SUD, so that they more frequently get involved in commitment to therapeutic goals and resist against use lapse (50).

Administration of sessions once a week has its own cons and pros. First benefit is that many of methamphetamine-dependent patients have financial problems and sometimes the therapeutic costs are provided by their families. Therefore, administration of *Regulated 12-Session Matrix Model*, would reduce treatment costs considerably and therefore, both probability of acceptance of treatment and probability of remain in the treatment would increase. The second benefit is that methamphetamine-dependent patients usually have degrees of depression and are low motivation and energy which may not allow patient to have proper capability to attend in therapeutic sessions twice a week and hence, one session a week would be more acceptable. It shall be noted that according to neuropsychological studies, methamphetamine abusers encounter structural and cognitive impairments which have adverse effects on therapeutic outcome. Damages to cingulate and insular cortices along with decline in functional integrity of hippocampus would confront these individuals with serious problems (51). Hence, successful therapeutic methods in methamphetamine abuse treatment (like Matrix Model) have special value to communities and societies.

Finding of the present study are considered as a new step towards adaptation and naturalization of *Regulated 12-Session Matrix Model* to SUD treatment in Iran, especially stimulant drugs and methamphetamine. It appears that with continuation of replication of such plan in various population sectors of the society, *Regulated 12-Session Matrix Model* would reach a brilliant situation in the process of secondary and tertiary prevention of SUD treatments. Moreover, implementation of modifications to the original Matrix treatment package, have made *Regulated 12-Session Matrix Model* to a flexible therapeutic method to be administered by formal and informal institutions, as well as NGOs which provide individuals with SUD and their families.

This study has reinforced the results of the previous study about utility of *Regulated 12-Session Matrix Model*(35) with assessment of both self-report and biological indicators of methamphetamine usage in methamphetamine dependents of Iran. It would be a great hope to successfully apply this method widely in Iranian and middle eastern methamphetamine dependents in order to reduce acute and chronic side effects of SUD on such populations. The sudden growth of methamphetamine use in Asia has emerged an agenda to formulate evidence-based practices to cope with such SUD in all three levels of prevention (21). Furthermore, with respect to the fact that in addition to high expenses of methamphetamine use to dependents and their families, the dependent individuals fail to

participate in productive and economic activities and impose their social and economic duties to others, any successful intervention would be beneficial to the individual, her/his family, community, and society to include their survived ex-substance dependent member to the routine practices and elevate the gross domestic product (GDP) rate as well. From another point of view, knowing that substance-dependent individuals are somehow withdrawn from society, effective treatments can increase social inclusion and solidarity with further social capital by augmentation and maximizing the cooperation of society members.

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