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ORIGINAL ARTICLE

Methylphenidate vs. resperidone in treatment of methamphetamine dependence: A clinical trial

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KEYWORDS

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Abstract *Background and aims:* Currently, there is no widely accepted evidence-based pharmacotherapy regime for the treatment of psychostimulant dependence. Yet, different pharmacological approaches have been tried in the treatment of MA addiction. The present study was conducted to compare efficiency of methylphenidate which is relatively easily accessible in our country, with resperidone for this purpose.

Methods: Eighty-six patients with MA dependence according to criteria defined by DSM IV-TR were divided into two groups. Patients in group R were given oral resperidone 1 mg daily for 1 week; then 2 mg daily in a divided dose for 3 weeks. Patients in group M were given oral methylphenidate 10 mg daily for 2 weeks, 7.5 mg daily for 1 week, then 5 mg daily for 1 week. They were evaluated for drug craving, psychological, neurologic and somatic symptoms at the start and end of the study.

Findings: Both drugs were useful for lowering drug craving in patients; however resperidone was more effective (6.31 ± 8.31 vs.19.6 ± 12.45 cravings per week, respectively). The effects of resperidone were more notable in lowering frequency and intensity of psychiatric, neurologic, cardiac and somatic symptoms of the patients after discontinuation of MA abuse; however methylphenidate was effective too; though with a lower potency.

Conclusion: The present study confirmed that both methylphenidate and resperidone can successfully be used for treatment of MA dependence, in order to reduce drug craving and psychological, neurologic, and somatic problems in patients. However, the efficacy of methylphenidate was estimated to be less than that of resperidone for this purpose.

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1. Introduction

The term "amphetamines" refers to a range of drugs related to amphetamine which share stimulant properties. Amphetamines can include amphetamine, methamphetamine,

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3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy"), methcathinone, and ephedrine. They are now the major illicit amphetamines available worldwide (Singleton et al., 2009). Methamphetamine (MA) is an indirect sympathomimetic agent that is distinguished from amphetamine by a more rapid distribution into the central nervous system (CNS), resulting in a rapid onset of euphoria that is the desired effect on those abusing the drug (Vearrier et al., 2012). Methamphetamine was first synthesized from ephedrine in 1893 by the Japanese scientist Nagai Nagayoshi, 6 years after the discovery of amphetamine (Panenka et al., 2012).

In several East Asian countries, methamphetamine is the most commonly used illicit drug, with recent data suggesting expanding markets in South Africa, Iraq and the Middle East. In Czech Republic and Slovakia, methamphetamine is the most commonly injected drug. Recent data from research studies suggest an increase in (injecting) the use of methamphetamine in Ukraine, Georgia, Armenia, and the Russian Federation (Singleton et al., 2009). The same trend has developed in Iran. An illicit drug with street name "Shisheh" has been dispensed among drug abusers in Iran whose main constituent is methamphetamine (Kazemifar et al., 2011). Its abuse has been recently popular in Iran with some dream like propaganda about its effect as a non-addictive drug (Kazemifar et al., 2011).

Methamphetamine abuse is a serious public health problem because of both costs associated with treatment of methamphetamine associated adverse health effects and crime and violence perpetrated to obtain methamphetamine or because of methamphetamine-related aggressive behavior (Vearrier et al., 2012).

Amphetamine dependence is characterized by an increased tolerance to the drug, withdrawal symptoms (sleep and appetite disturbances, fatigue, depression, irritability, craving, depression, anxiety or agitation), and inability to reduce drug use despite significant negative social, health and psychological problems associated with such use; as stated in DSM IV TR (Pérez-Mañá et al., 2012). There is currently no widely accepted evidence-based pharmacotherapy regime for the treatment of psychostimulant dependence (Schifano 2011; Srisurapanont et al., 2001). However, different pharmacological approaches have been tried in the treatment of MA addiction. The most conventional drugs include antidepressants, antipsychotics and substitution/replacement therapies. The critical role of dopamine neurotransmission in the psychostimulant and addictive properties of MA and other amphetamines has driven research on the efficacy of dopamine D2 receptor antagonists (i.e., antipsychotics) as potential treatments for stimulant abuse (Panenka et al., 2012). Opioid antagonists or agonists have also been suggested for drug therapy in MA dependence or other stimulants (Mooney et al., 2013; Penetar, 2012).

The prescription stimulant methylphenidate also exhibits potential for the treatment of MA addiction. The use of psychostimulants to treat amphetamine dependence or abuse is based on previous successful results of replacement therapy in other disorders such as nicotine or opiate dependence (Pérez-Mañá et al., 2012). By definition, medications used as maintenance therapy should have similar properties (mechanism of action, behavioral effects) to the abused drug, but less addictive potential. Psychostimulants may substitute the use of amphetamines by reducing amphetamine withdrawal and craving and therefore, leading to abstinence (Pérez-Mañá et al., 2012; White, 2000). Case studies of amphetamine dependence in subjects without psychiatric comorbidity have reported that methylphenidate provided long-term help for MA use (Panenka et al., 2012).

The present study was conducted to evaluate the efficacy of methylphenidate as a prescribed drug for treatment of MA dependence and compare it with resperidone an atypical antipsychotic which is also a candidate for treatment of MA dependence.

2. Materials and methods

The studied individuals were randomly selected from persons with MA dependence according to criteria defined by DSM IV-TR who had referred to a rehabilitation clinic in a university teaching hospital, Arak city, Iran in 2012. The other inclusion criteria were positive urine test for MA, negative history of abuse of other drugs and alcohol, and age between 18–65 years. If any patient had history of any major organic diseases, use of antipsychotic or mood changing drugs, any mental illnesses, suicidal ideation, pregnancy or lactation, and sensitivity to methylphenidate or resperidone, he/she was excluded from the study. All the studied patients provided informed consent for participation to the study. The study had been approved by local ethical committee of Arak's university of medical sciences. It was registered in database of Iranian clinical trials (reg. no.: IRCT201202159018N1).

86 patients were enrolled into the study. They were randomly divided into two groups with equal size. The patients in the first group were given oral resperidone 1 mg daily for 1 week; then 2 mg daily in a divided dose for 3 weeks. The patients in the second group were given oral methylphenidate 10 mg daily for 2 weeks, 7.5 mg daily for 1 week, then 5 mg daily for 1 week.

The patients were visited by a physician every week. They were evaluated for drug craving, psychological, neurologic and somatic symptoms at the start and end of the study.

The collected data were analyzed by SPSS software version 16.0. Differences between the groups were determined by *T*-test and chi-square test. Statistical significance was set at *p*-value less than 0.05.

3. Results

73 Patients including 35 in methylphenidate group (group M) and 38 in resperidone group (group R) completed their treatment course. The remaining 13 (eight in group M and five in group R) were excluded due to failure to follow the recommended treatment regime. General characteristics of the groups are shown in Table 1. All of the patients were smoking the drug. No oral or injection route for use of the drug was seen. 31 patients (14 in group M and 17 in group R) had no previous attempts for treatment of their abuse.

Patients in group M had weight gain during the study (2.40 ± 1.037 kg). Patients in the other group had weight gain too (2.47 ± 1.042 kg). Their difference was not statistically significant (p-value = 0.9). A comparison of groups for drug craving before and after the study is shown in Table 2. The difference between groups was not statistically significant before the study (p-value = 0.6); but was notable after the end of the study (p-value = 0.002).

Table 1 General characteristics of the studied groups.

	Group M $n = 35$	Group R $n = 38$	p-Value
Age	34.12 ± 7.27	30.35 ± 7.68	0.20
Sex:			
Male	32	32	0.31
Female	3	6	
Blood pressure:			
Systolic	123 ± 10.11	132 ± 10.98	0.34
Diastolic	83 ± 8.75	86 ± 8.65	0.31
Pulse rate	87 ± 8.55	90 ± 8.78	0.25
Respiratory rate	18 ± 1.2	19 ± 1.3	0.21
Body temperature (centigrade)	37.1 ± 0.32	37.0 ± 0.34	0.30
Body weight (kg)	65.3 ± 13.06	64.8 ± 13.89	0.20
Daily dose of the drug (grams)	1.27 ± 0.86	1.24 ± 0.77	0.18
Frequency of drug use per day	5.93 ± 3.72	5.88 ± 3.64	0.22

Table 2 The drug craving in studied group before and after the study.

	Drug craving (number of cravings per week)	
	Before the study	At the end of the study
Group R	38.43 ± 24.38	6.31 ± 8.31
Group M	41.33 ± 23.32	19.6 ± 12.45

The presence of psychiatric symptoms and signs including nervousness, panic attack, visual or tactile hallucination, delusion, suicidal ideation or attempt, obsessive thoughts or acts, increased daily activities, irritability, excitability, verbalism, insomnia, and anxiety was evaluated in patients. Severity of complaints had been scored from 0–5, as judged by the examining physician. The result is demonstrated in Table 3. The difference between groups was statistically significant (p-value = 0.0001).

Presence and severity of neurologic problems including tremor, convulsion, dizziness, altered level of consciousness, athetotic movements, speech disorders, and numbness in extremities were evaluated in the studied patients by physician and were scored from 0–5. The scores were 33.17 ± 6.72 and 33.27 ± 6.78 in groups R and M, respectively before the study; which changed to 19.73 ± 3.50 and 28.47 ± 5.60 correspondingly at the end of the study. The changes were statistically significant (p-value = 0.0001).

Patients were evaluated for cardiovascular related problems consisting of dyspnea, chest pain, hypertension, tachycardia, and palpitation. Each problem would be scored from 0–5 by a physician; if present. The scores were 11.13 ± 5.14 and 12.37 ± 4.39 in groups R and M respectively before the study; which changed to 7.83 ± 3.30 and 10.80 ± 3.49 in that order at the end of the study. The difference between groups was statistically significant (p-value = 0.001).

Table 3 Severity of psychiatric symptoms and signs in studied group before and after the study.

	Degree of severity of psychiatric symptoms and signs	
	Before the study	At the end of the study
Group R	58.33 ± 9.24	35.73 ± 5.90
Group M	58.80 ± 13.47	52.6 ± 12.80

The presence of somatic symptoms including midriasis, xerostomia, pruritus, acne, any other skin lesion, change in appetite, and alteration in body temperature was also assessed in patients. They were scored from 0 to 5 by the examining physician. The scores of the patients were 19.37 ± 5.69 and 19.40 ± 7.79 in groups R and M, respectively before the study. The scores were 13.47 ± 5.07 and 17.97 ± 7.35 in the groups R and M, respectively at the end of the study. The difference between groups was statistically significant after the end of the study (p-value = 0.008).

4. Discussion

The present study confirmed that both methylphenidate and resperidone can successfully be used for treatment of MA dependence, in order to reduce drug craving and psychological, neurologic, and somatic problems in patients. However, the efficacy of resperidone was estimated to be higher than that of methylphenidate for this purpose.

Indirect evidence supports a rationale for the use of antidepressants – particularly those with a serotonergic mechanism of action, based on efficacy in preclinical models, clinical efficacy in treating compulsive behavior, and potential for ameliorating the affective symptoms of stimulant withdrawal. However, most studies with antidepressants have not found clinically meaningful benefits of these drugs on a range of MA abuse-related measures, including drug craving (Panenka et al., 2012; Shoptaw et al., 2006). Heinzerling and his colleagues have reported discouraging results in their study conducted to evaluate the efficacy of Bupropion for treatment of MA dependence in adolescents (Heinzerling et al., 2013), though it had been recommended for MA dependence with moderate drug use in an earlier study (Brensilver et al., 2012).

Despite a decade of intensive research, effective pharmacotherapy for stimulant dependence remains elusive; with a noted lack of controlled clinical trials studying methamphetamine abuse in particular (Ma et al., 2012).

The dysregulation of dopamine (DA) transmission has been a focus of studies on mechanisms of addiction. However, capitalizing on this knowledge has not yet produced effective pharmacotherapies (Graves et al., 2012). There is also evidence to suggest contributions of glutamatergic neurotransmission to MA taking and relapse behaviors (Kufahl et al., 2013), however its clinical implications remain to be determined.

Non-amphetamine psychostimulants such as modafinil have been studied for treatment of MA dependence too; with promising results (Anderson et al., 2012).

Due to lack of a hopeful drug effective in the treatment of MA dependence, the present study was conducted to compare the efficiency of methylphenidate which is relatively easily accessible in our country, with that of resperidone for this purpose.

There are few related published studies to be compared. Laqueille and his coworkers have reported 4 cases of MA dependence treated with methylphenidate, however all four were 50–60 years old (Laqueille et al., 2005). Tiihonen and his colleagues have compared methylphenidate with aripiperazol for treatment of MA dependence, however their study has ended prematurely and all of their patients were IV abuser; yet their results have been promising (Tiihonen et al., 2007).

Similarly, the current study confirmed that methylphenidate is a relatively effectual drug for treatment of psychiatric, neurologic, and somatic signs and symptoms after discontinuation of MA abuse and decline in drug craving; in comparison with currently recommended drugs, such as resperidone.

The starting dose of methylphenidate was 10 mg per day. Possibly, the use of a higher dosage to overcome cross-tolerance between MA and methylphenidate will lead to more effective results. It can be examined in future studies.

In summary, results of the present study showed that methylphenidate can be used in treatment of MA dependence; however its effect seems to be less than that of resperidone.

Conflict of interest

None.

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