Adding extended-release methylphenidate to psychological intervention for treatment of methamphetamine dependence: A double-blind randomized controlled trial

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Abstract

Background: Iran has been faced with an emerging epidemic of methamphetamine (MA) use during recent years. No effective pharmacotherapy has been identified for MA treatment; and psychological interventions are the only available effective treatment. The aim of this study is to investigate the efficacy and safety of extended-release methylphenidate (ER-MTP) for the treatment of methamphetamine dependence.

Methods: Sixty-two people with methamphetamine dependence, according to DSM-IV-TR, were randomly assigned to either fixed-dose extended-release methylphenidate (ER-MTP) (60 mg per day) or placebo for 12 weeks. All participants received twice-weekly cognitive behavioral treatment for stimulant dependence. Recent drug use and craving level were measured using weekly rapid urine test and craving visual analogue scale, respectively. The severity of addiction was measured using the Addiction Severity Index at baseline and study completion. Assessment of MA withdrawal was conducted using Amphetamine Withdrawal Questionnaire and Amphetamine Selective Severity Assessment at baseline, day 3, week 1, week 4 and week 12. Depression and high-risk behaviors assessed with the Beck Depression Inventory and the high-risk behavior questionnaire at baseline, weeks 4 and 12 of the study. SPSS software version 22 was used for data analysis and $p<0.05$ was considered significant.

Results: Percent of weekly MA negative urine tests was not significantly different between groups during the course of the study ($p=0.766$). Two groups showed similar retention rates. Changes in MA craving, withdrawal, addiction severity, depression and high-risk behaviors were not significantly different between groups. No serious adverse event was observed.

Conclusion: Our finding did not show the superiority of fixed-schedule ER-MTP over placebo when added to an intensive biweekly outpatient psychosocial treatment. Further studies using individually tailored flexible-dose regimes might provide new insights regarding the safety and efficacy of psychostimulant maintenance treatment for MA dependence.

Keywords: Methamphetamine, Amphetamine-Related disorders, Treatment, Methylphenidate

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↑*What is "already known" in this topic:*
No effective pharmacotherapy has been found for stimulant dependence yet. Preclinical studies support the potential efficacy of agonist-like maintenance treatment with methylphenidate (MTP) for methamphetamine (MA) dependence. Previous controlled clinical studies suggest positive trends for MTP in MA treatment.

→*What this article adds:*
Adding-on a fixed-dose extended-release methylphenidate treatment regime to intensive psychological treatments was not superior to placebo in treatment retention, weekly MA negative urine test, and craving outcomes. Further studies to explore the effect of dose and treatment regime on treatment efficacy are needed.

Introduction

Annual prevalence of last year amphetamines use estimated to be 0.7% in 2016 globally (1). For centuries, opioids have been the main drug of use in Iran drug scene (2), although a methamphetamine (MA) use epidemic has emerged in the country during the last decade (3). MA use rapidly spread in the country as a result of positive outcome expectations and low perceived risk (4) and treatment demand for MA treatment was increased (3).

Among illicit drugs, amphetamines are the second leading factor attributable to the burden of disease after opioids at the global level (5). MA use is associated with an increased risk for cardiovascular diseases, psychiatric disorders, injecting, and sexual-related high-risk behaviors and mortality (3, 6-8). MA use is associated with an increased risk for psychosis, anxiety, depression, suicidal ideation, suicidal attempts, and problems with controlling anger and violence (6-7).

No pharmacological treatment has been introduced for MA use disorder (9), and psychosocial treatments are the only identified effective interventions (10, 11). Using agonist maintenance treatments has been successful for the treatment of opioids (12, 13) and tobacco use disorders (14). Evidence regarding the efficacy of agonist treatments for stimulant (MA) use disorder is limited (15).

It has been shown that stimulants' use is associated with brain dopaminergic system deficits (16), as a result of reactive species formation (17). However, using psychostimulants has a dose-dependent impact on extracellular dopamine concentrations (18). There is a distinct pattern of post-synaptic dopamine receptors' activation and potential neurotoxic effects among those use stimulants for therapeutic purposes compared to people who use high doses often seen in stimulant addiction (18-21).

Pre-clinical studies support methylphenidate (MTP) as a potential candidate for the agonist-like treatment of stimulant dependence (15, 22). MTP is a psychostimulant medication, which has been approved for the treatment of attention deficit hyperactivity disorder (ADHD) among children, adolescents (23) and adults (24). A Finish study showed the superiority of slow-release MTP (SR-MTP) (54mg/day) over placebo on MA abstinence outcomes among people with amphetamine or MA dependence that use drugs through injection (25). A more recent study in Finland and New Zealand did not find any differences between extended-release MTP (ER-MTP) (54mg/day) and placebo on treatment retention and MA abstinence outcomes, although ER-MTP treatment was associated with higher retention rate as compared to placebo from week 6 to 22 of the study (26).

As a result of preliminary positive trends for MTP, the aim of this randomized controlled trial (RCT) is to evaluate the efficacy of extended-release MPH (ER-MTP) compared to placebo for MA dependence.

Methods
Design

The study was a 12-week phase II, parallel groups, randomized, placebo-controlled trial of ER-MTP added to standard psychological treatment of MA dependence.

Participants

Inclusion criteria were age 18 to 65 years old, diagnosis of MA dependence according to DSM-IV-TR (27), positive rapid urine test for MA, and voluntary informed written consent for the treatment. Exclusion criteria were current diagnosis of other substance use disorders (except nicotine), current or past history of other axis I psychiatric disorders (except depression), having a significant risk of suicide or violence to others, significant neurologic or medical diseases, pregnancy and lactation, history of childhood ADHD, development of psychotic symptoms required pharmacotherapy and IQ lower than 70. Eligibility of the study participants was determined through an interview conducted by the study physician.

Recruitment and Consent

Participants were recruited from treatment-seeking patients referring to Mehrayeen outpatient specialized drug treatment center in Tehran from September 2013 to June 2016. The recruitment methods included the announcement of the study among medical doctors of other drug treatment centers and asked them to refer potential participants to the study. Patients who referred to the study site and sought MA dependence treatment were screened for eligibility criteria.

Allocation, Concealment, and Blinding

Participants (n=62) randomized to receive either ER-MTP (n=32) or placebo (n=30) using random sequence blocks with a block size of 4 generated by Microsoft Excel software. Concealment of allocation was performed using sequentially numbered, opaque, and sealed envelopes. Treatment providers of the drug treatment center were all blinded to the treatment group throughout the study.

Interventions

Study participants received either ER-MTP or placebo through the same size, color and shape gel capsules filled with ER-MTP (20mg; Stimdate®, manufactured by Mehrdarou Pharmaceutical Company) in the active arm or starch in the placebo arm. MPH dose was ER-MPH 20mg (once a day at morning) for week 1, 40mg (20mg twice a day at morning and noon) for week 2 and 60mg (20mg thrice a day at morning, noon and afternoon) for weeks 3 to 12. All participants were visited twice weekly by the study physician in the morning. At visit days, participants were requested to take their morning doses under the direct supervision of the dispensing nurse. Study participants were allowed to receive other doses as take-home in childproof pill containers. Study participants received medication-adherence and safety psychoeducation by the treatment team including study physician and clinical psychologist. They were informed that their medication is scheduled and diverting their doses results to exclusion from the trial.

All participants also received individual treatment sessions based on the modified Matrix model twice a week by

a trained clinical psychologist. Modified Matrix treatment for stimulant treatment is a structured treatment consisted of 24 sessions using motivational enhancement, psychoeducational and cognitive, behavioral treatment techniques (28).

All treatment interventions and assessments were provided free of charge. Potential benefits and adverse effects of study participation were clearly explained for participants, and informed written consent was obtained. It was explained to participants that they could exit from the study whenever they want and this would not have any negative effect on receiving routine services from the study site. The study protocol and questionnaires were approved by the Ethics Committee of Vice-Chancellor for Research, Tehran University of Medical Sciences (TUMS) (Code: 16507). The study was registered in Iranian Registry of Clinical Trials (registration code: IRCT201202281556N38)

Measures

A physical exam was carried out by study physician at baseline. Urine sample was tested for methamphetamine (manufactured by ACON, cut-off point for minimal sensitivity of 500 ng/ml) on a weekly basis. A pregnancy test was conducted for female participants at baseline. Eligible participants were randomized to receive either ER-MTP or placebo after providing informed written consent.

A comprehensive history of drug and alcohol use and severity of problems in medical, psychiatric, employment and family domains were measured by Addiction Severity Index (ASI)-5th Edition at baseline and week 12 (29). Farsi version of ASI-5th Edition has shown good reliability and validity (30). ASI composite score (CSs) for each functional domain was calculated using the ASI manual; with higher scores represent higher addiction severity. Methamphetamine withdrawal was measured using Amphetamine Withdrawal Questionnaire (AWQ) (31) and Amphetamine Selective Severity Assessment (ASSA) (32) at baseline and day 3-4, week 1, week 4 and week 12. AWQ is a 10-item questionnaire measuring MA withdrawal severity over the previous 24 hours. Each item scored on a four-point Likert-type scale, from 0 (not at all) to 4 (very much). ASSA is an 18-item questionnaire which used to provide information on a broader range of MA withdrawal. ASSA items score from 0 to 7, with higher scores indicated greater severity. A preliminary analysis of our data showed that Cronbach's alpha coefficients for AWQ and ASSA were excellent (91%) and good (84%), respectively. The highest degree of craving during the last 24 hours was measured with a visual analogue scale (VAS) on a weekly basis (33). VAS is a single-item assessment in which participants were asked to rate their highest level of MA craving during the last 24 hours on a 10 cm ruler graded from 0 to 100 (33-34). We used beck depression inventory- second edition (BDI-II) to measure depression (35). The Farsi version of BDI-II has shown acceptable reliability and validity (36). To measure injecting and sexual-related high-risk behaviors, we used standard Iranian bio-behavioral survey questionnaires for people who use drugs (37-39) at baseline, weeks 4 and 12. Study questionnaires were completed by a trained master level clinical psychologist. Blood pressure of participants

and adverse effects were monitored on a weekly basis by the study physician.

Outcomes

Primary outcomes of the study were percent of the weekly negative urine tests for MA measured by a rapid urine test, addiction severity and craving. The secondary outcome measures were treatment retention, self-report of MA use, self-report of using other drugs, methamphetamine withdrawal, depression, high-risk behaviors and adverse events.

Sample size

Assuming a clinically significant between-group differences of 15% on a weekly negative urine test, a standard deviation of 20%, a power of 80% and a two-sided significance level of 0.05, a minimal sample size of 58 was calculated. Considering the high attrition rate, we increased the planned sample size to 70.

Data analysis

SPSS software version 22 (IBM Corp, Armonk, NY) was used for data analysis. We used intention to treat analysis to compare treatment outcomes between groups. Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number and percentage. To compare groups in terms of treatment retention, and urine test results for MA, analysis of variance (ANOVA), generalized linear model (GLM) was used. Generalized estimating equation (GEE) was used for between-groups comparison of craving. ANOVA was used to compare groups differences in terms of depression, withdrawal and high-risk behaviors outcomes.

Results

Among 161 of clients referred to the study site, 62 met eligibility criteria. The eligible participants were randomized to ER-MTP (n=32) and placebo (n=30). Among 62 study participants who received at least one dose of study medication, 31 (50%) completed 12 weeks of study. The retention rate for ER-MTP and placebo groups were 53.13% and 46.67%, respectively. Flow diagram of the study was presented in Figure 1.

Demographic characteristic

The average age of participants in intervention and control groups was 31.9 (±2.77) and 32.33(±3.48) years, respectively. Female participants in intervention and control groups were 28.1% and 30%, respectively. Baseline demographic characteristics of participants in control and intervention groups did not show significant differences at baseline assessment (Table 1).

History of drug use

History of MA use, use of other drugs, severity of depression, CSs of ASI domains including medical, employment, alcohol, drug, family, legal and psychiatric domains did not have significant differences between groups at baseline assessment (Table 1).
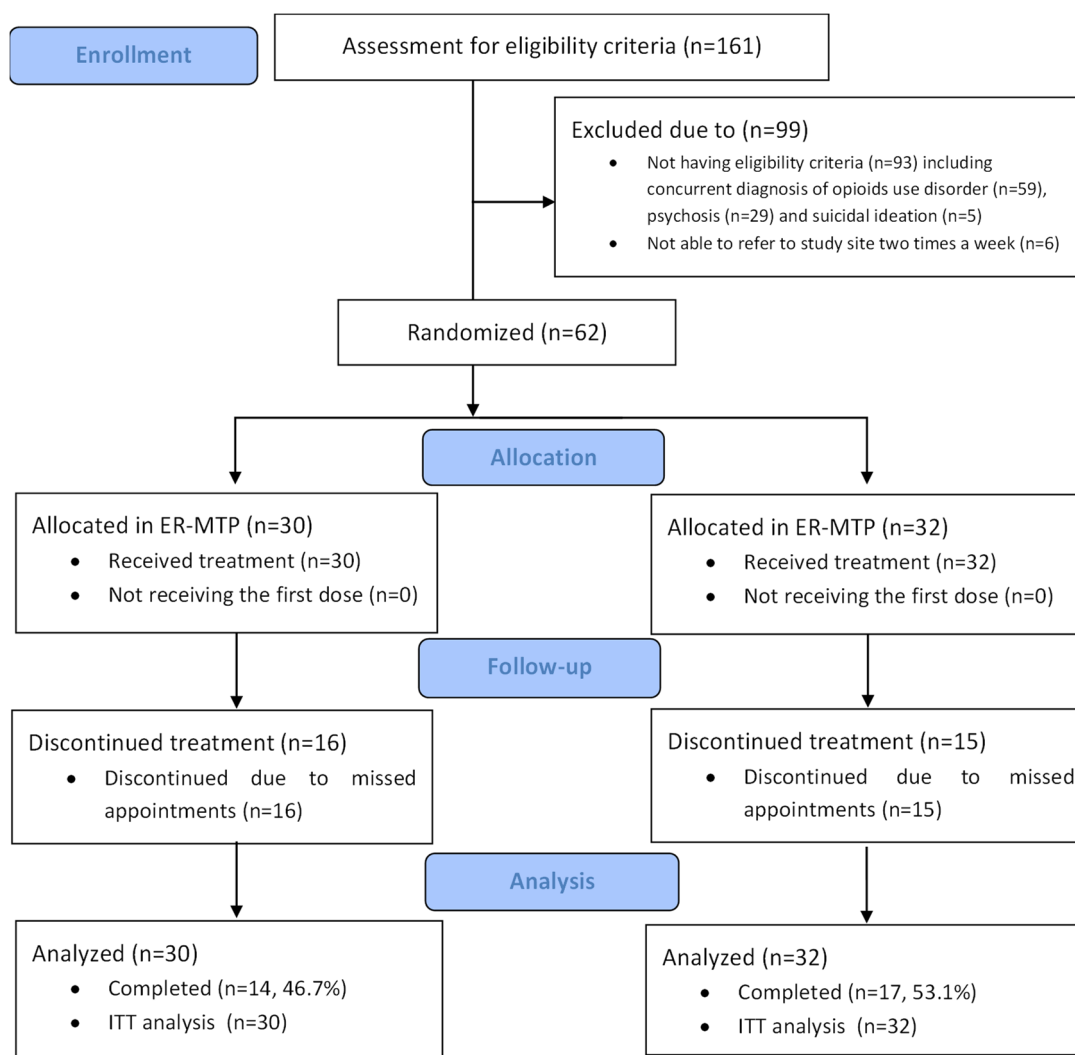
Fig. 1. CONSORT diagram

Treatment retention

Treatment retention in ER-MTP and placebo groups was 53.1% and 46.7%, respectively. Retention rate as a categorical variable compared between groups using GLM analysis and did not show significant differences between groups (p=0.610) (Fig. 2).

MA abstinence

Percent of positive MA urine tests did not show significant differences between study groups during the 12 weeks of the study, using GLM analysis (p=0.766) (Fig. 3). Terminal abstinence defined as the percentage of negative MA urine tests between groups at week 12. There was a trend toward better abstinence rate in ER-MTP (82.4%) compared to placebo (78.6%), although the difference between groups was not significant (p=0.215). The average number of MA use days during the last month in the ER-MTP group (1.35±1.41) was not significantly different from the placebo group (1.29±1.14) (p=0.887). Differences between the reduction in the average number of MA use days during the last month in the ER-MTP group (27.94±2.49) were not significant with the placebo group (28.29±1.90) (p=0.673).

Abstinence of other drugs

Changes in self-report of the number of days using drug and alcohol during last month at baseline and week 12 were not significantly different between groups (Table 2).

Craving: Highest level of craving during the last 24 hours was not significantly different between groups at baseline (ER-MTP: 44.38±10.6, placebo: 44.67±9.6 p=0.887). Mean changes in craving scores during the course of study did not show a significant difference between groups using GEE (p=0.525).

Withdrawal

Withdrawal scores measured by AWQ (ER-MTP: 5.7±3.3 placebo: 5.944±29 p=0.682) and ASSA (ER-MTP: 19.16±8.3, placebo: 19.80±9.6 p=0.783) did not have a significant difference at baseline. Methamphetamine withdrawal measured by AWQ and ASSA decreased significantly in both groups during the study; however, between-

Table 1. Demographic characteristics of participants, history of drug use, CSs of ASI domains and depression at baseline

	Study group		p
	ER-MTP	Placebo	
Demographic chracteristics			
Age	31.90 (±2.77)	32.33 (±3.48)	0.645
Gender			
• Male	71.9%	70.0%	0.574
• Female	28.1%	30.0%	
Marital status			
• Married	62.5%	49.3%	0.234
• Divorced	21.9%	20.0%	
• Never married (signle)	15.6%	30.7%	
Completed years of eduction	11.8 (±1.6)	11.4 (±2.3)	0.735
Occupational status			
• Full-time	59.4%	46.7%	0.343
• Part-time	21.8%	23.3%	
• Unemployed	18.8%	30%	
Living status (with whom)			
• With family	90.6%	96.7%	0.491
• With friends	3.1%	0.0%	
• Alone	6.3%	3.3%	
Place of residence owned by participants or their families			
• Yes	34.4%	30.0%	0.734
• No	65.6%	70.0%	
Having valid car license			
• Yes	78.1%	86.7%	0.125
• No	21.9%	13.3%	
Drug Use History			
Years of regular methamphetamine use	5.7 (±1.3)	5.1 (±1.8)	0.712
Days of methamphtamine use during last month	29.6 (±1.5)	29.8 (±1.1)	0.836
Year of regular opium use	1.5 (±1.5)	1.2 (±1.2)	0.431
Days of opium use during last month	3.1 (±3.9)	2.1 (±3.1)	0.532
Year of regular heroin use	0.7 (±1.1)	0.9 (±1.3)	0.281
Days of heroin use during last month	0	0	1
Years of regular alcohol use	0.1 (±0.3)	0.1 (±0.3)	0.821
Days of alcohol use during last month	1.1 (±2.2)	1.2 (±1.8)	0.782
Days of alcohol use at intoxication level during last month	0.7 (±1.3)	0.6 (±1.2)	0.751
Years of regular sedatives use	0.3 (±0.5)	0.3 (±0.5)	0.842
Days of sedative use during last month	4.1 (±3.9)	3.1 (±3.8)	0.421
Years of regular cannabis use	1.1 (±1.1)	1.3 (±1.2)	0.421
Days of cannabis use during last month	2.9 (±3.5)	4 (±5.1)	0.195
Years of polysubstance use	0.9 (±0.8)	1.0 (±1.0)	0.743
Days of polysubstance use last month	8.5 (±4.5)	8.3 (±5.9)	0.839
Addiction severity composite scores			
Medical	0.14 (±0.12)	0.13 (±0.98)	0.775
Employment	0.37 (±0.25)	0.39 (±0.27)	0.634
Alcohol	0.05 (±0.09)	0.06 (±0.10)	0.491
Drug	0.55 (±0.02)	0.54 (±0.03)	0.743
Legal	0.04 (±0.17)	0.11 (±0.25)	0.161
Familial	0.48 (±0.10)	0.52 (±0.14)	0.576
Psychiatric	0.39 (±0.13)	0.40 (±0.15)	0.761
Beck depression inventory score	18.3 (±8.5)	18.4 (±8.3)	0.656

group comparisons did not find significant differences in changes in AWQ (F=0.533 p=0.225) and ASSA (F=0.425 p=0.325) scores.

ASI CSs

Both groups showed a significant decrease in ASI CSs for medical, drug, family and psychiatric domains at week 12 as compared to baseline, although the differences between groups were not significant. CSs for alcohol and legal domains were very low for both groups at baseline and did not show a significant decrease at week 12. The change in CSs at baseline and 12 weeks follow-up was not significantly different between ER-MTP and placebo groups (Table 2).

Depression

Severity of depression was measured by BDI-II in the ER-MTP group was 18.3 (±8.5) at baseline which was decreased to 13.4 (±4.7) and 9.6 (±2.4), respectively. BDI-II score in the placebo group was 18.4 (±8.3) at baseline which was decreased to 12.2 (±5.1) and 9.7 (±1.9) at weeks 4 and 12, respectively. Depression scores at week 12 both in ER-MTP and placebo groups, were significantly lower than baseline (p=0.001). The change in depression scores in the course of study was not significantly different between groups (F=0.376, p=0.544).

High-risk behaviors
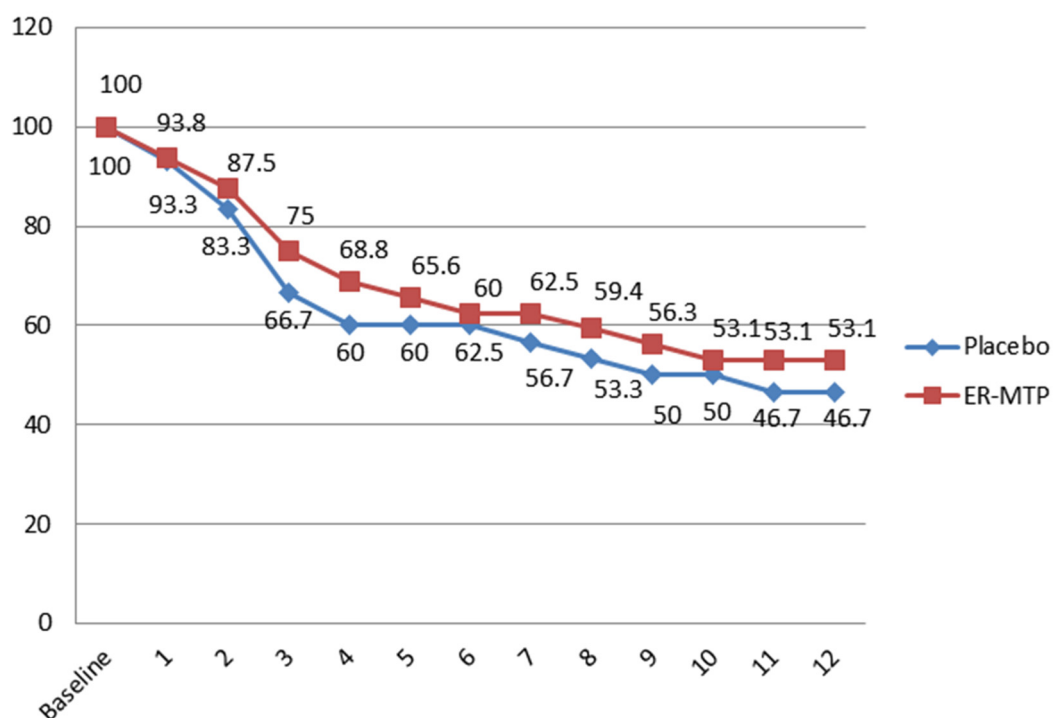
HIV-related high-risk behaviors questionnaire consisted
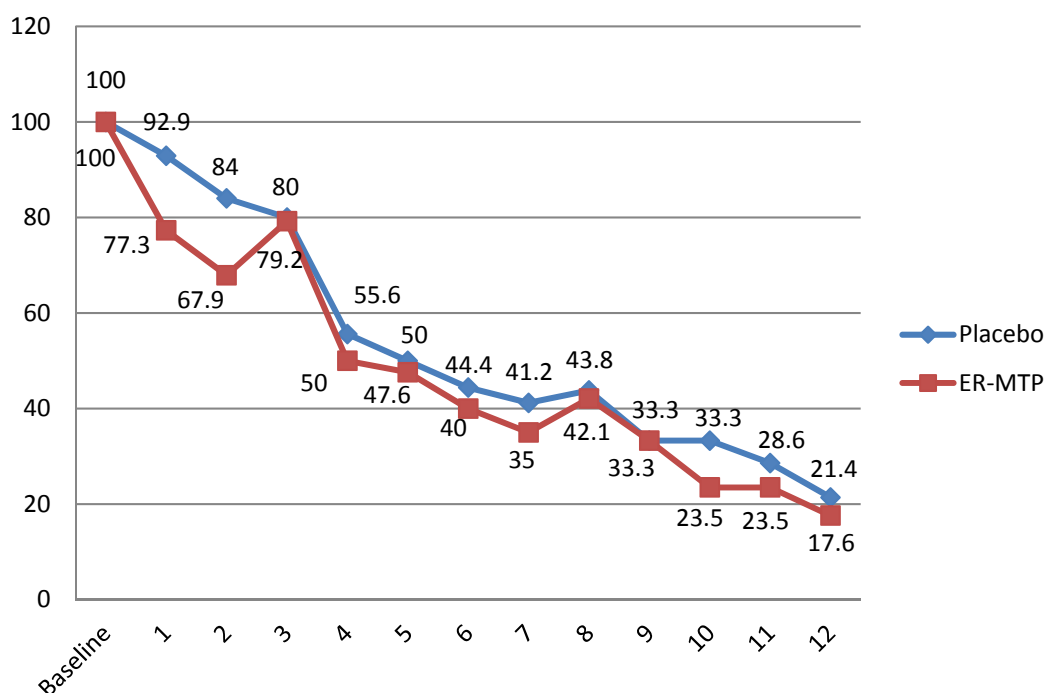
Fig. 2. Retention rate by study groups

Fig. 3. Percent of positive weekly urine tests

of items measuring injecting and unprotected inter-course during last month. The participants did not accept any history of injection during last month at baseline and weeks 4 and 12 follow-ups. The average number of sexual intercourses during last month in ER-MTP at baseline assessment was 6.9 (±5.6) which decreased to 5.7 (±4.0) and 4.1 (±2.9) at weeks 4 and 12, respectively. The average number of sexual intercourses was significantly decreased

in the ER-MTP group in week 12 as compared to baseline (p<0.001). The average number of sexual intercourses in the placebo group at baseline was 7.0 (±6.1) and decreased to 4.7 (±3.9) and 3.8 (±2.9) at 4 and 12 weeks follow-up, respectively. Reduction in the average number of sexual in-tercourses as compared to baseline assessment significantly decrease (p=0.000). The comparison of groups in terms of the average number of sexual intercourses during the study

Table 2. Self-report of using other drugs and CSs of ASI at baseline and week 12

	Baseline		Week 12		p
	ER-MTP	Placebo	ER-MTP	Placebo	
Drug use history					
Days of opium use during last month	3.1 (±3.9)	2.1 (±3.1)	0.1 (±0.2)	0.1 (±0.5)	0.566
Days of heroin use during last month	0	0	0	0	1
Days of alcohol use during last month	1.1 (±2.2)	1.2 (±1.8)	0.6 (±0.8)	0.6 (±0.9)	0.955
Days of alcohol use at intoxication level during last month	0.7 (±1.3)	0.6 (±1.2)	0.3 (±0.6)	0.2 (±0.6)	0.708
Days of sedative medications use during last month	4.1 (±3.9)	3.1 (±3.8)	1.2 (±1.7)	1.0 (±1.5)	0.759
Days of cannabis use during last month	2.9 (±3.5)	4 (±5.1)	2.2 (±3.2)	2.5 (±6.3)	0.854
Days of polysubstance use	8.5 (±4.5)	8.3 (±5.9)	7.9 (±4.8)	7.3 (±4.9)	0.981
ASI Composite Scores (CSs)					
Medical	0.14 (±0.12)	0.13 (±0.98)	0.07 (±0.08)	0.08 (±0.10)	0.425
Employment	0.37 (±0.25)	0.39 (±0.27)	0.34 (±0.18)	0.37 (±0.24)	0.812
Alcohol	0.05 (±0.09)	0.06 (±0.10)	0.04 (±0.01)	0.05 (±0.07)	0.781
Drug	0.55 (±0.02)	0.54 (±0.03)	0.15 (±0.03)	0.14 (±0.04)	0.433
Legal	0.04 (±0.17)	0.11 (±0.25)	0.04 (±0.08)	0.09 (±0.08)	0.278
Familial	0.48 (±0.10)	0.52 (±0.14)	0.08 (±0.06)	0.15 (±0.08)	0.202
Psychiatric	0.39 (±0.13)	0.40 (±0.15)	0.10 (±0.07)	0.15 (±0.07)	0.336

was not significantly different (p=0.753).

The average number of sexual intercourse without a condom during last months at baseline was 2.9 (±2.1) which decreased to 2.3 (±1.4) and 1.5 (±1.0) at week 4 and 12 follow-ups and at week 12 of the follow up was significantly lower than the baseline (p<0.001). The variable in the placebo group at baseline was 3.6 (±2.1) and decreased to 1.8 (±1.3) and 1.4 (±0.9) at weeks 4 and 12 follow-ups and the decrease as compared to baseline was significant (p=0.000). Although both groups showed a significant decrease in the number of sexual intercourse during the last month without condom, between groups comparison did not reveal a significant difference during 12 weeks study (p=0.533).

Percent of unprotected sex during last month in the ER-MTP group at baseline was 44.5% which was decreased to 36.7% and 24.5% at weeks 4 and 12 follow-ups, respectively and the decrease in the variable at week 12 as compared to baseline was significant (p=0.001). Similarly, percent of unprotected sex during last month in the placebo group was decreased from 47.3% at baseline to 25.5% and 25% at weeks 4 and 12, respectively and the decrease in the variable from baseline to week 12 was significant (p=0.001). Although both groups showed a significant decrease in the percent of unprotected sex during the last month, between groups comparison, did not find a significant difference between groups (p=0.225).

Percent of participants who reported not using condoms in their last sex in the ER-MTP group was 68.8% which was decreased to 54.5% and 29.4% at weeks 4 and 12 follow-ups, respectively, and decrease in the variable at weeks 12 as compared to baseline was significant (p=0.001). In placebo group also percent of participants who reported not using a condom in their last sex was decreased from 56.7% at baseline to 33.3% and 28.6% at weeks 4 and 12 follow-ups, respectively and the change in the variable at week 12 was significant as compared to baseline (p=0.001). The change in percent of participants who report not using a condom in their last sexual intercourse was not significantly different between study groups (p=0.345).

Side effects

No serious side effects, including suicide attempt, aggression, psychosis or chest pain was not seen. The monitoring of blood pressure did not show an increase in blood pressure above the normal range in any participant. There was no report of an overt attempt of study participants to sell study medication in clinic premises; therefore, no participant was excluded from the study due to diversion of study medication. A range of side effects including insomnia, headache, dizziness, anxiety, dysphoria, decreased appetite, muscle aches, nausea and irritability were observed among study participants, but all were mild and did not necessitate discontinuation of study medication.

Post-hoc analysis

Figure 3 shows that there was a separation between ER-MTP and placebo groups with regard to percent of weekly MA positive urine tests in week 1 and 2. Although the change in percent of weekly MA urine tests did not show significant between-groups differences over the course of study, a post-hoc analysis showed that a decrease in the percent of MA positive urine test during the first 2 weeks of study in ER-MTP was significantly higher than the placebo group (p= 0.019). ER-MTP group also showed significantly lower craving scores during the first 2 weeks of the study (p=0.001). Significantly lower severity of withdrawal measured by AWQ (p=0.024) and ASSA (p=0.020) in the first week of the study (baseline, day 3 and week 1 assessments) was evident in ER-MTP group as compared to placebo.

Discussion

Study results did not find the superiority of ER-MTP (60mg/day) over placebo in percent of negative weekly urine tests, terminal abstinence and self-report number of MA use during last month during 12 weeks of study, although both groups showed a significant decrease in mentioned outcomes as compared to baseline. Although the percent of participants who completed the study was higher in the ER-MTP group as compared to placebo but the difference was not statistically significant.

These results were consistent with findings of an RCT comparing slow-release dexamphetamine (110 mg/day) with placebo during 12 weeks in Australia (40), in which

both groups showed a significant decrease in MA use, although between groups comparisons could not find significant differences. A 12-weeks open-label comparison of dexamphetamine treatment (60mg/day) with placebo also did not show a significant difference between groups in terms of weekly negative urine tests, the cost paid for MA and HIV-related high-risk behaviors (41). An 8-weeks RCT in San Fransisco, US on the efficacy of slow-release dexamphetamine (30mg twice a day) also did not show significant between-groups differences in treatment retention, self-reported MA use and negative urine test for MA (42). Two RCTs comparing the efficacy of osmotic-release oral system MTP (54mg/day) with placebo among people who inject MA/amphetamines (25) and people with MA dependence (43), reported significantly lower MA positive urine test in ER-MTP group compared to placebo, although two other RCTs could not replicate these results (26, 44).

Inconsistent outcomes on MA negative urine between studies using psychostimulant maintenance treatment approaches might be the result of different medication adherence across studies. Further studies to measure the effect of medication adherence on treatment outcomes are warranted.

Our finding showed no significant differences in treatment retention between the study groups, which was consistent with the results of previous studies using dopamine agonist maintenance treatment including slow-release dexamphetamine (30 mg twice a week) (42) and ER-MTP (54mg/day) (25, 26, 43, 44), although one RCT reported higher retention rate in slow-release dexamphetamine group (individually tailored up to 110mg/day) as compared to placebo (40). This suggests the importance of investigating the safety and efficacy of individualized regimes of dopamine maintenance treatments for MA use. One RCT showed a significantly higher retention rate in ER-MTP (54mg/day) group compared to the placebo group from week 6 to week 22 (26). Further studies with higher sample sizes and longer follow-up are needed to investigate long term treatment efficacy of ER-MTP.

In our study, the decrease in weekly craving scores throughout of study was not significantly different between groups which was consistent with two ER-MTP vs. placebo RCTS for 22-weeks (26) and 14 weeks (44), respectively. However, it was inconsistent with the result of another RCT for 10-weeks which only measured carving at three time points including baseline, week 6 and 10 (43). Our study and all other mentioned RCTs used a fixed schedule dose regime of ER-MTP. Experimental studies have shown higher serum levels of methadone (45, 46) or buprenorphine (47) are associated with lower craving levels among people with opioid use disorder. A finding which supported with clinical studies showing higher methadone (48, 49) and buprenorphine doses (12, 50) are associated with more illicit opioid use abstinence in opioid agonist maintenance programs. Further studies are needed to investigate the effect of different doses and treatment regimens on MA craving.

Change in withdrawal severity scores over the course of study was not significantly different between groups, although the post-hoc analysis of our results showed that during the first week of the study, participants in the ER-MTP group reported significantly lower levels of withdrawal severity as compared to placebo. These findings were consistent with the results of an RCT comparing the efficacy of an individualized dose regime of slow-release dexamphetamine (up to 110mg per day) among people with MA dependence (40). Likewise, participants in the active treatment group showed significantly more reduction in withdrawal scores at the end of the stabilization phase (first 14 days) compared to the placebo. A trend toward more reduction in withdrawal was seen in the slow-release dexamphetamine group, although it was not significant over the course of study.

The post-hoc analysis also showed a significantly more reduction in the percent of MA positive urine test and craving during the first 2 weeks of study in the ER-MTP group as compared to the placebo. A study on the natural course of withdrawal and craving among people with MA dependence indicated that acute phase of MA withdrawal lasts for 7-10 days after MA cessation, although MA craving levels will remain high for weeks and months (51). Our findings suggest that the potentially positive effect of ER-MTP might be mediated through alleviating withdrawal severity during the first 2 weeks of treatment, but its effect has been disappeared after passing of the high initial peak of withdrawal. A similar pattern has been reported with low, fixed-dose opioid agonist maintenance treatments, which could effectively manage withdrawal signs and symptoms and increase short-term abstinence but could not significantly improve long-term abstinence over placebo (12).

We did not see any serious side effects in study groups, a finding which was consistent with previous studies using ER-MTP (25, 44) or other psychostimulants (40, 42) for MA treatment.

Limitations of this study include a small sample size that limits subgroup analysis based on gender or addiction severity and high attrition rate. Treatment retention was not significantly different between groups; it suggests that reasons for attrition are not related to study medication.

Conclusion
Our findings showed that fixed-schedule ER-MTP treatment for MA dependence was safe. Although ER-MTP treatment was more effective than placebo on MA negative urine test, withdrawal and craving during weeks 1 and 2; it did not significantly improve treatment retention, abstinence, craving and withdrawal during the 12-week course of the study. Further studies using individualized, flexible-dose regimes might provide new insights regarding the effect of psychostimulant maintenance treatment for MA dependence.

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