



## Research paper

# Mental health and cognitive function responses to quetiapine in patients with methamphetamine abuse under methadone maintenance treatment



Najme Sadat Javdan<sup>a</sup>, **Fatemeh Sadat Ghoreishi<sup>b,c</sup>**, Mojtaba Sehat<sup>d</sup>, Amir Ghaderi<sup>a</sup>,  
Hamid Reza Banafshe<sup>e,f,\*</sup>

<sup>a</sup> Department of Addiction studies, School of Medical, Kashan University of Medical Sciences, Kashan, Iran

<sup>b</sup> Clinical Research Development Unit-Matini/Kargarnejad Hospital, Kashan University of Medical Sciences, Kashan, Iran

<sup>c</sup> Department of Psychiatry, School of Medicine, Kashan University of Medical Science, Kashan, Iran

<sup>d</sup> Department of Community Medicine, Kashan University of Medical Sciences, Kashan, Iran

<sup>e</sup> Department of Pharmacology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran

<sup>f</sup> Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran

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## ABSTRACT

**Background:** Patients with methamphetamine (MA) abuse under methadone maintenance treatment (MMT) are susceptible to several complications including cognitive disturbance and mental health disorder. This trial was designed to determine the impacts of quetiapine administration on cognitive function and mental health scale in patients with MA abuse under MMT.

**Methods:** This study was carried out in 60 MA abusers under MMT. Patients were randomly allocated to receive either 100 mg quetiapine ( $n = 30$ ) or control ( $n = 30$ ) daily for 8 weeks. Cognitive function and mental health scale were taken at baseline and post-treatment to evaluate relevant variables.

**Results:** Quetiapine significantly decreased depression ( $b -3.94$ ; 95% CI,  $-7.73, -0.16$ ;  $P = 0.04$ ) and sleep disorder ( $b -2.18$ ; 95% CI,  $-2.89, -1.47$ ;  $P < 0.001$ ). Also, quetiapine administration resulted in a significant reduction in Iowa Gambling Task ( $b -2.70$ ; 95% CI,  $-4.69, -0.71$ ;  $P = 0.009$ ), and significant increases in Verbal Fluency Test ( $b 3.04$ ; 95% CI,  $1.24, 4.85$ ;  $P = 0.001$ ), Reverse Digit Span ( $b 2.80$ ; 95% CI,  $2.13, 3.47$ ;  $P = 0.001$ ) compared with the placebo.

**Conclusion:** Overall, taking 100 mg quetiapine daily for 8 weeks by patients MA abuse in MMT had favorable effects on some of cognitive functions and mental health parameters.

## 1. Introduction

methamphetamine (MA) is a psycho-stimulant drug with highly addictive characteristics (Ghaderi et al., 2017b; Mehrjerdi et al., 2014). Recently, MA abuse has become a health concern in the Iranian population (Massah and Moradi, 2018). Research findings demonstrated that recent years, the MA abuse increased from 3.9% to 89.5% among women and 60.3% among men in Iran (Alammehrjerdi et al., 2018). MMT improves social functioning and quality of life (Dolan et al., 2003). However, despite the extensive and successful implementation of the MMT, many challenges and obstacles remain. Recently, MA dependence increased among patients under MMT (Noori et al., 2016). The MA dependence enhance trend over time which may provide a lack of consideration to untreated MA dependence in the cases with MMT

(Alammehrjerdi et al., 2018). This problem due to self-treatment for mental health dysfunction in patients under MMT (Alam Mehrjerdi et al., 2013; Ghaderi et al., 2018; Massah and Moradi, 2018). Patients MA abuse under MMT have some psychiatric problems such as cognitive impairment (Potvin et al., 2018; Wang et al., 2017), depression and anxiety symptoms (Glasner-Edwards et al., 2009, 2010) and sleep disturbances (Ghaderi et al., 2017a; Mahoney et al., 2014). Recently, various psychosocial interventions (e.g., technology-based treatments, Matrix Model and cognitive-behavioral therapy) have been employed in the treatment of cases with MA dependence (Minozzi et al., 2016; Tait et al., 2015). Despite several attempts, there is no the approved pharmacotherapy platform for MA dependence therapy yet (Phillips et al., 2014).

Quetiapine, a new antipsychotic drug, has associated with favorable

**Abbreviations:** BDI, beck depression inventory; BAI, beck anxiety inventory; DGSP, digit span; DGSP-straight, straight digit span; DGSP-reverse, reverse digit span; IGT, Iowa gambling task; TMT, trial making test; TMT-A, trial making test-form A; TMT-B, trial making test-form B; PSQI, pittsburgh sleep quality index

\* Corresponding author at: Department of Pharmacology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran.

E-mail address: [banafshe57@hotmail.com](mailto:banafshe57@hotmail.com) (H.R. Banafshe).

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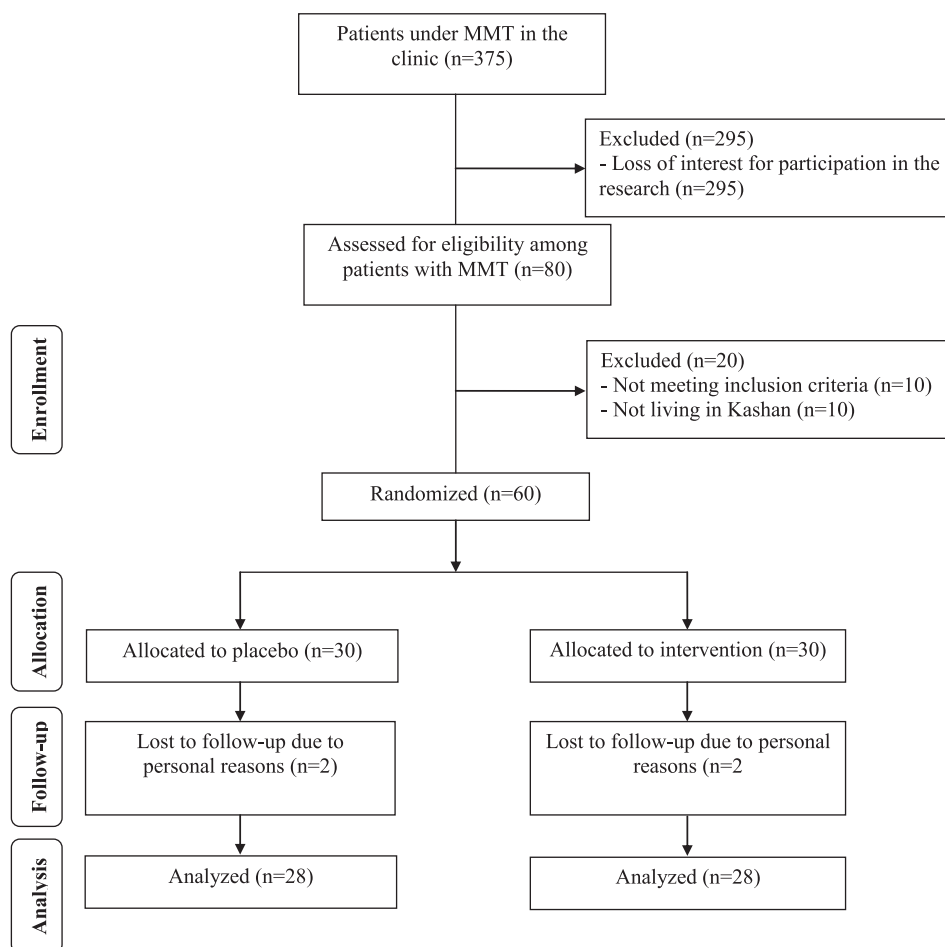


Fig. 1. Summary of patient flow.

effects on negative and positive symptoms, and cognitive disturbance in chronic schizophrenia (Purdon et al., 2001). Some researches documented that quetiapine may reduce the anxiety score and improve sleep quality (Kapur et al., 2000), cognitive impairment and depression symptoms (Baune, 2008). Several studies showed the favorable effects of quetiapine on mental health, and cognitive function. In the study by Sattar et al. (2004), it was documented that consuming 50 mg/day to a maximum of 300 mg/day quetiapine (average 153 mg/day) for 28 day in patients with coexisting substance dependence disorders had favorable effects on sleep, anxiety. Also, previous studies showed that quetiapine intake at a dosage of 50–100 mg/day to people with bipolar disorder and cocaine dependence had beneficial effects on psychiatric symptoms (Brown et al., 2002). In addition, recently studies demonstrated that administration of quetiapine improves verbal short-term memory, inhibition abilities and positive parameters in patients psychosis (Urban et al., 2012), and memory in animal models (He et al., 2006). However, quetiapine compared to olanzapine did not improve learning, memory, attention and working memory or cognitive functions in an adolescent population (Robles et al., 2011).

Quetiapine is known as an atypical neuroleptic and D<sub>2</sub> antagonist. It has been showed that this drug has a high affinity for serotonin, histamine and  $\alpha$ 1-adrenergic receptors, while has a low affinity for dopamine receptors (Kondo et al., 2013). It has been showed that quetiapine exerts its roles via decreasing of dopamine blockade, which could result in the reduction of drug abuse. Moreover, the dopamine receptors could be blocked by quetiapine in the limbic system that lead to improvement of minimal blockade role of dopamine in the reward system. Subsequently, quetiapine enables to bind to histamine H1 receptors and induction relaxation, which can also enhance the cognitive

function and mental health (Purdon et al., 2001; Samiei et al., 2016; Sattar et al., 2004). Despite the well known therapeutic effects of quetiapine, the impacts of quetiapine on cognitive function, depression and anxiety in cases with MA abuse under MMT are restricted. We considered that the utilization of quetiapine in patients with MA abuse under MMT might be provided for elevating the quality of life and reducing the side effects. Thus, in the current research, the effects of quetiapine intake on mental features including cognitive function and mental health in MA abuse under MMT cases were assessed.

## 2. Methods

### 2.1. Trial design

This study was registered in the Iranian website for registration of clinical trials at <http://www.irct.ir>: IRCT20171106037290N1, the Primary Registry in the WHO Registry Network set up in collaboration with Ministry of Health and Medical Education. This study was conducted among 60 MA abuse under MMT, aged 18–65 years who were referred to the Golabchi Clinic in Kashan, Iran. The research ethics committee of Medical Science department at Kashan University estimated and approved the study protocol (IR.Kaums.REC.1396.123). This scientific experiment was carried out in accordance with the Declaration of Helsinki. All participants filed their agreement to take part in this study. All consent forms were reviewed by the research ethics committee of Medical Science department at Kashan University.

**Table 1**  
General characteristics of the study participants<sup>a</sup>.

	Placebo group (n = 28)	Quetiapine group (n = 28)	p <sup>b</sup>
Age (y)	38.7 ± 10.0	37.1 ± 9.0	0.68
Height (cm)	169.2 ± 7.5	170.6 ± 6.5	0.14
Weight at study baseline (kg)	74.8 ± 11.9	74.4 ± 11.7	0.38
Weight at the end-of-trial (kg)	72.1 ± 10.5	72.3 ± 9.2	0.46
Weight change (kg)	-0.39 ± 2.1	0.14 ± 2.5	0.40
BMI at study baseline (kg/m <sup>2</sup> )	26.2 ± 4.2	24.8 ± 3.5	0.18
BMI at the end-of-trial (kg/m <sup>2</sup> )	26.0 ± 4.2	24.8 ± 3.1	0.23
BMI change (kg/m <sup>2</sup> )	-0.13 ± 0.7	0.05 ± 0.8	0.37
Education (%)			
Illiterate	3 (10.7)	4 (14.3)	
Elementary	11 (39.3)	10 (35.7)	
Intermediate	14 (50)	13 (46.4)	0.74 <sup>†</sup>
Diploma	0 (0)	1 (3.6)	
Marital status (%)			
Single	12 (42.9)	10 (35.7)	
Married	7 (25)	6 (21.4)	0.70 <sup>†</sup>
Widow/Divorced	9 (32.1)	12 (42.9)	
Job (%)			
Unemployed	24 (85.7)	21 (75)	
Employed	0 (0)	2 (7.1)	0.31 <sup>†</sup>
Others	4 (14.3)	5 (17.9)	
Use of other drugs (%)			
None	23 (82.2)	19 (67.8)	
Sedative-Hypnotic	2 (7.1)	5 (17.9)	0.40 <sup>†</sup>
Antidepressants	3 (10.7)	4 (14.3)	
Age of the first MA experience	32 ± 7.8	32.6 ± 8.6	0.77
Dose of MA use (g/week)	0.59 ± 0.4	0.47 ± 0.4	0.29
Frequency of MA use (week)	3.2 ± 1.4	2.7 ± 1.4	0.17
Duration of MA use (y)	2.2 ± 1.0	2.5 ± 1.1	0.33
Methadone dose (mL/d)	17.3 ± 4.4	18.9 ± 5.4	0.23
Duration of MMT (y)	5.5 ± 2.0	6.1 ± 2.1	0.28

<sup>a</sup> Data are mean ± SDs.

<sup>b</sup> Obtained from independent t-test.

<sup>†</sup> Obtained from Pearson Chi-square test.

**2.2. Inclusion criteria**

The included subjects were aged 18–65 years, with history of MA and opioid co-abuse in the past year and currently undergoing methadone maintenance treatment, evaluated by the drug abuse section of the Structured Clinical Interview for DSM-IV, Seeking treatment for MA abuse.

**2.3. Exclusion criteria**

The excluded subjects were suicide efforts history within the past

**Table 2**  
The effect of quetiapine on mental health, and cognitive function parameters in methadone maintenance treatment patients.

Variables	Placebo group (n = 28)		Quetiapine group (n = 28)		Difference in outcome measures between quetiapine and placebo treatment groups <sup>a</sup> b (95% CI)	p <sup>b</sup>
	Baseline	Week 8	Baseline	Week 8		
BAI	16.4 ± 4.2	16.8 ± 4.0	18.2 ± 6.4	17.2 ± 5.5	-0.31 (-2.81, 2.17)	0.79
BDI	20.1 ± 6.7	20.1 ± 8.7	20.5 ± 5.6	17.1 ± 5.5	-3.94 (-7.73, -0.16)	0.04
PSQI	6.3 ± 1.9	6.4 ± 2.3	6.7 ± 2.2	4.3 ± 1.6	-2.18 (-2.89, -1.47)	<0.001
IGT	26.4 ± 5.1	27.5 ± 4.1	25.89 ± 4.6	24.1 ± 6.1	-2.70 (-4.69, -0.71)	0.009
TMT subscales						
TMT-A	20.6 ± 3.0	21.8 ± 4.0	21.5 ± 2.4	20.8 ± 2.5	-1.07 (-2.77, -0.62)	0.20
TMT-B	51.7 ± 6.4	50.7 ± 4.9	50.6 ± 5.4	49.3 ± 4.9	-1.45 (-4.27, 1.35)	0.30
Verbal fluency test (FAS test)						
Numbers of total words	32.8 ± 3.2	33.9 ± 3.2	33.7 ± 2.9	37.4 ± 3.4	3.04 (1.24, 4.85)	0.001
DGSP						
DGSP-straight	8.9 ± 1.5	9.3 ± 1.3	9.1 ± 1.7	9.8 ± 1.2	0.40 (-0.18, 0.98)	0.17
DGSP-reverse	7.9 ± 1.1	7.8 ± 1.4	8.3 ± 1.0	10.7 ± 0.8	2.80 (2.13, 3.47)	0.001

Data are mean ± SDs.

<sup>a</sup> "Outcome measures" refers to the change in values of measures of interest between baseline and week 8. b [difference in the mean outcomes measures between treatment groups (quetiapine group = 1 and placebo group = 0)].

<sup>b</sup> Obtained from multiple regression model (adjusted for baseline values age and baseline weight).

one years or either psychotic scale in the past 24 weeks or suicidal ideations as considered, cocaine and major cardiovascular disturbance, alcohol dependence, metabolic diseases (e.g., neurological diseases and diabetes).

**2.4. Study design**

Participation were randomized into both groups and received either 100 mg quetiapine (Tadmir Kala Jam trading Company, Tehran, Iran) or placebo (Barij Essence, Kashan, Iran) (n = 30 each group) daily for 8 weeks. The lack of document on the suitable dosage of quetiapine in treatment of MA and opioid co-abuse resulted in we employed the above-stated dosage of quetiapine based on a recently published report in subjects with cocaine dependence and bipolar disorder (Brown et al., 2002; Telles-Correia et al., 2017). The dosage form of administered methadone was syrup. All patients completed three physical activity and 3-day food records as metabolic equivalents (METs) (Ainsworth et al., 2000) at weeks 0, 2, 4, 6 and 8 of the intervention.

**2.5. Blinding**

Placebo and quetiapine tablets were made in the same way. These tablets had identical shape, size, color, texture, and odor. Placebo quetiapine tablets were obtained in the same container with a code numeral. The tablets were made by Zahravi, Tabriz, Iran. Hence, participation, physician, and other agents were all blind to the intervention group assignments.

**2.6. Randomization**

Randomization assignment was accomplished using computer-generated random numbers and was done by a trained staff at the clinic as blindness.

**2.7. Safety**

The included subjects were invited to tell agents about all side-effects during the intervention. The clinical signs were considered and assessed at the initiation and at each base-line visit. Moreover, potential complaints were considered with telephone call every day and the physician and psychiatrists were responsible for discontinuing or continuing the taking tablets.

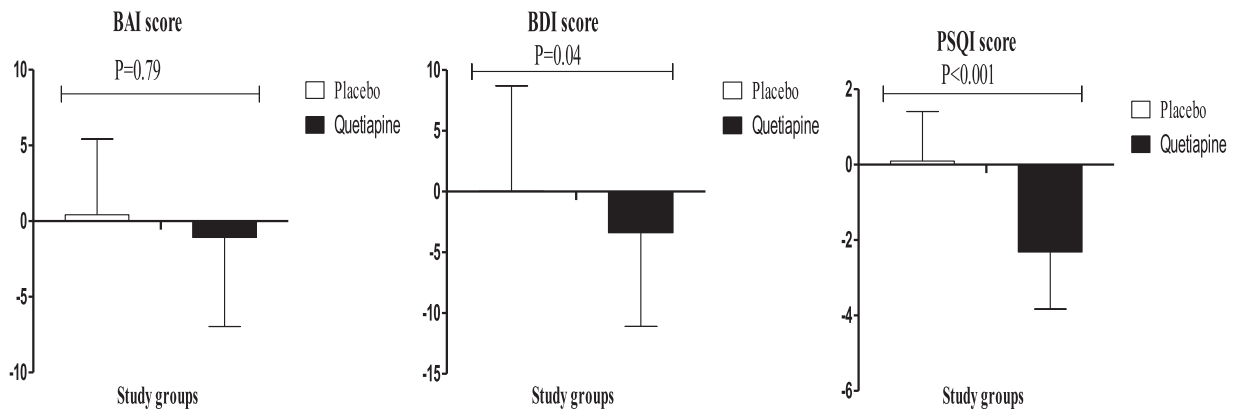


Fig. 2. Change (means ± SDs) in BAI, BDI and PSQI score in patients MA abuse under MMT receiving quetiapine and placebo. P value was obtained from independent *t*-test. *N* = 28 in each group.

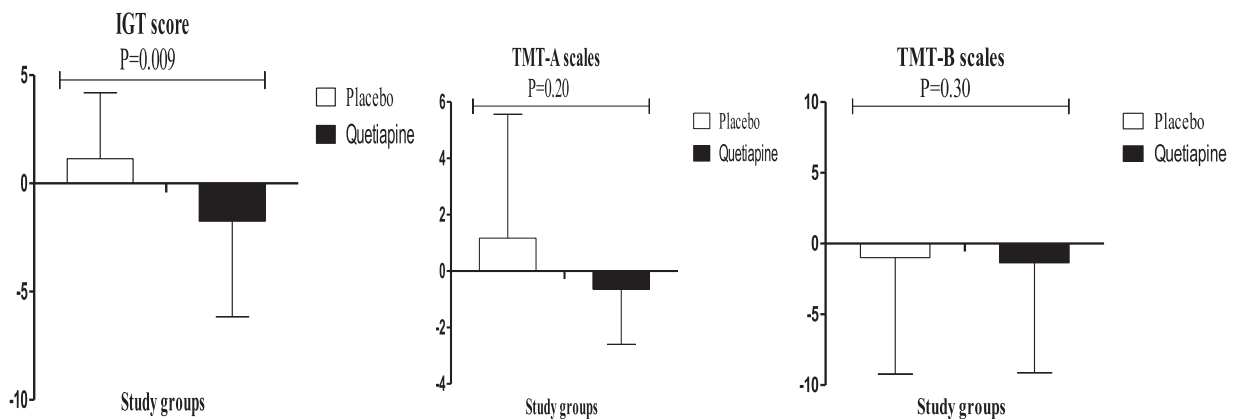


Fig. 3. Change (means ± SDs) in IGT score, TMT-A and TMT-B scales in patients MA abuse under MMT receiving quetiapine and placebo. P value was obtained from independent *t*-test. *N* = 28 in each group.

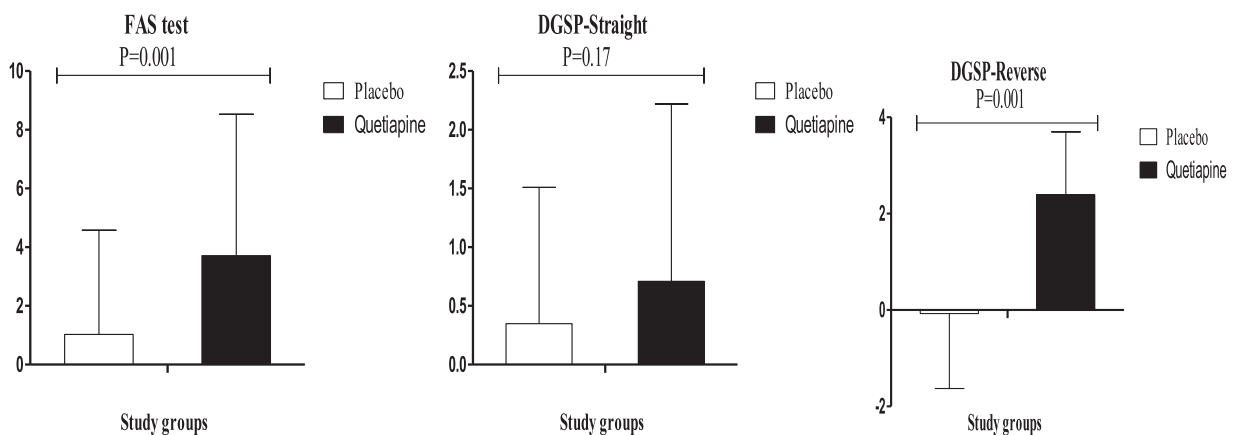


Fig. 4. Change (means ± SDs) in FAS test, DGSP-straight and DGSP-Reverse in patients MA abuse under MMT receiving quetiapine and placebo. P value was obtained from independent *t*-test. *N* = 28 in each group.

### 2.8. Anthropometric scale

Anthropometric measures of cases were established using a standard scale (Seca, Hamburg, Germany) at start the intervention and 2 months after intervention.

### 2.9. Clinical measures

#### 2.9.1. Mental health

Beck Depression Inventory (BDI) was assessed using a self-compiled

questionnaire (Buysse et al., 1989). Quality of sleep was determined using Pittsburgh Sleep Quality Index (PSQI) (Beck et al., 1961). Anxiety parameters measured by Beck Anxiety Inventory (BAI) that developed by Beck et al. (1988) to determine the frequency of anxiety scales in young people and adults.

#### 2.9.2. Cognitive functions

Trail Making Test (TMT) is normally administered in two sub-components that are known as TMT-A and TMT-B (Lamberty et al., 1994; Stuss et al., 2001). TMT measures several cognitive tasks (e.g.,

visual search and scanning, attention, sequencing and shifting, abstraction, cognitive flexibility and psychomotor speed) (Salthouse, 2011). TMT is normally administered using two sub-components which are found as TMT-A and TMT-B. In TMT-A, the subjects is accessible with encircled numbers from 1 to 25 randomly distributed on a sheet of paper, and they are instructed to link the numbers in ascending order (i.e., 1-2-3...) applying a pencil or pen. In TMT-B is known as a second sheet which is included both letters and encircled numbers and that the subjects should link in alternating ascending order (i.e., 1-A-2-B-...). Task performance in each section is common quantified by obtaining the completion time, with TMT-B taking longer to complete. IOWA gambling task (IGT) is a useful tool for analyzing the individuals' decision making process. The participants were faced with four cards. The first two cards offer higher prizes but sometimes give the participants some negative points as well. On the other side, the last two cards offer less amounts of money but their probability of losing was far less than two others (Businelle et al., 2008; Turnbull et al., 2014). Short-term auditory memory was measured by Digits spans backwards in Wechsler intelligence Scale (DGSP). The patients read a list of three to nine digits calmly and loudly, and the subject should read them in the same way after listening to each list. This test, which is one of the most commonly used index of intelligence, requires that the subject reciprocate some of the lists of read digits in the same way and others. In the first case, memory is for direct cultivars, and in the second case, memory for the invertible variables is measured (Jasinski et al., 2011; Pilgrim et al., 1999). The Verbal Fluency Test (FAS test), a subtest of the Neurosensory Center Comprehensive Examination for Aphasia (Crockett, 1977) is a measure of phonemic word fluency, which is a type of verbal fluency. It assesses phonemic fluency by requesting an individual to orally produce as several words as possible that begin with the letters F, A, and S within a prescribed time frame, usually 1 min.

### 2.10. Sample size

Sample size was calculated based on the primary outcomes and using the results of a prior study (Katzman et al., 2011) in which  $s_1$ ,  $s_2$ ,  $\mu_1$  and  $\mu_2$  of the anxiety score in the placebo and quetiapine groups were respectively 0.24, 0.21, 1.90, and 1.76. Type one ( $\alpha$ ) and type two errors ( $\beta$ ) were defined as 0.05, and 0.20, having the study power of 80%, the sample size was estimated at 22 subjects for each group; based on allowing for dropouts in each group, the final sample size was considered to be 30 participants in each group.

### 2.11. Statistical analysis

The normality of data distribution was assessed using Kolmogorov-Smirnov test. Independent sample *t*-test was applied to determine the differences in anthropometric measures and dietary intakes between the two intervention groups. Multiple linear regression models were used to assess treatment effects on study outcomes after adjusting for confounding variables including the baseline values of outcomes as well as age and BMI at baseline. The effect sizes were reported as the mean differences via 95% confidence intervals. Bootstrapping was also used as a sensitivity analysis of confidence intervals and inverse probability weighting was used to account for loss-to-follow-up, but the results did not change substantially. The *P*-values of  $<0.05$  were considered statistically significant.

## 3. Results

Two participants in the treatment and placebo groups dropped out for personal reasons. Eventually, 56 patients [quetiapine ( $n = 28$ ) and placebo ( $n = 28$ )] completed the study (Fig. 1). The compliance rate in our trial was high; more than 90% of capsules were administration during the trial in both groups. No serious side effects were reported following the administration of quetiapine in patients MA abuse.

Although, grade 1 adverse events were reported in 7 cases in the quetiapine group [headache ( $n = 3$ ), drowsiness ( $n = 3$ ) and vertigo ( $n = 1$ )], no patients was excluded in this trial.

Mean age, BMI, weight, height, education, marital status, job, use of other drugs, age of the first MA experience, dose of MA use, frequency of MA use, duration of MA use, methadone dose and duration of MMT were not significantly different among quetiapine and control groups (Table 1).

Quetiapine significantly reduced BDI ( $b -3.94$ ; 95% CI, -7.73, -0.16;  $P = 0.04$ ) and PSQI ( $b -2.18$ ; 95% CI, -2.89, -1.47;  $P < 0.001$ ) (Table 2).

Patients who received quetiapine had a significant reduction in IGT ( $b -2.70$ ; 95% CI, -4.69, -0.71;  $P = 0.009$ ), and significant increases in Verbal Fluency Test ( $b 3.04$ ; 95% CI, 1.24, 4.85;  $P = 0.001$ ), DGSP-Reverse ( $b 2.80$ ; 95% CI, 2.13, 3.47;  $P = 0.001$ ) (Table 2). Quetiapine administration did not change other cognitive functions and mental health parameters. Changes in BDI score, BAI score, PSQI score, IGT score, TMT-A scales, TMT-B scales, FAS test, DGSP-Straight and DGSP-Reverse score in patients MA abuse under MMT receiving quetiapine and placebo are presented in Figs. 2–4.

## 4. Discussion

We evaluated the impacts of quetiapine administration for 8 weeks on mental health parameters and cognitive functions in patients with MA abuse under MMT. Our study demonstrated that administration quetiapine for 8 weeks, compared with the placebo, improved BDI, PSQI, IGT, FAS, DGSP-Reverse, but did not affect BAI, TMT subscales, and DGSP-Straight. Based on these findings, quetiapine may an appropriate adjunct therapy for patients with MA and opioid co-abuse. To our knowledge, this trial for the first time evaluated the effects of quetiapine on mental health parameters and cognitive functions of patients with MA with MA and opioid co-abuse.

### 4.1. Effects on mental health

Patients with MA abuse under MMT are susceptible to many psychological disturbances, such as sleep, anxiety, and depression (Ghaderi et al., 2017a; Glasner-Edwards et al., 2009; Glasner-Edwards et al., 2010; Mahoney et al., 2014). We found that quetiapine intake to patients MA abuse in MMT for 8 weeks improved depression and sleep indexes, yet did not affect anxiety indices. It should be considered that in the present report, subjects were matched based on dosage of methadone. However, we think that this can not affect on our results because subjects in both non-intervention and intervention were receiving methadone. Hence, the considered pharmacological impacts on depression and sleep can be due to receiving quetiapine. This must be taken into account in the understanding of our results. Several studies have investigated the effects of quetiapine on mental health parameters in participants without MA abuse under MMT, though the results are controversial. Baune (2008), observed that quetiapine intake (range 50–300 mg/day) for 8 weeks can play a significant role in the management of major depressive disorder (MDD) and general anxiety. In addition, taking quetiapine (average 153 mg/day) for 28 day by patients with coexisting substance dependence disorders had beneficial effects on sleep, anxiety, and depression (Sattar et al., 2004). Monnelly et al. (2004) also found that quetiapine at a dosage of 20–200 mg/day improved sleep disturbance in alcohol dependence. In another study, quetiapine administration (flexible doses, 50–800 mg/day) for 16 weeks had significant efficacy on psychiatric symptoms (Martinotti et al., 2008). The impact of quetiapine in treating psychological symptoms disturbance leads to the view that it is a multi-functional psychoactive drug. It's a wide range of effect is likely due to its ability to alter systems of noradrenergic, serotonergic and dopaminergic and its efficacy appear to be mediated via the actions of nor-quetiapine and quetiapine (Altamura et al., 2012).



## 4.2. Effects on cognitive function

MA abuses under MMT were associated with increased cognitive disturbance (Potvin et al., 2018; Wang et al., 2017). Our study supported that consuming quetiapine for 8 weeks by patients with MA abuse under MMT significantly improved IGT, FAS, and DGSP-Reverse, but did not affect TMT subscales, and DGSP-Straight. Although data presenting the effects of quetiapine on cognitive function in MA abusers under MMT are scarce, the effects of quetiapine on cognitive function in other patients have been evaluated. In an animal study by He et al. (2006), it was shown that the intake of quetiapine had ameliorated the effects of MA on cognitive and memory impairment in rats. Also, Purdon et al. (2001) found that quetiapine intake were associated with a better general cognitive, verbal reasoning and fluency after 6-month treatment. Furthermore, receiving quetiapine (mean dose was  $350 \pm 213$  mg/days) for 12 weeks was related to improves cognitive function and positive scale in patients episode psychosis (Urban et al., 2012). Moreover, the enhancement of cognitive function after using quetiapine have been considered to be higher than those observed in treatment resistant patients who received clozapine (Buchanan et al., 1994). However, quetiapine compared to olanzapine did not influence cognitive, learning and memory in an adolescent population (Robles et al., 2011). The absence of significant effect of quetiapine on TMT subscales, and DGSP-Straight might be explained through using different trial designs, different dosages of quetiapine used as well as different characteristics of participants. The effects of quetiapine on cognitive function maybe mediated through inducing acetylcholine release (Ichikawa et al., 2002; Samiei et al., 2016). Acetylcholine is found that a very important neurotransmitter which is related to learning and memory consolidation. It has been showed that the increasing concentrations of acetylcholine could lead to the improvement of memory. Moreover, quetiapine is able to reduce the immobilization stress-induced via modulating BDNF expression. And this drug enables to enhance neuroplasticity though over expression of BDNF (Fumagalli et al., 2004). BDNF prompts the induced neuronal death by METH (Matsuzaki et al., 2004) that has a critical role in the related memory parts (i.e., social recognition memory and spatial memory) (Broad et al., 2002). Future evidences need to evaluate the beneficial effects of quetiapine related genes (e.g. BDNF) in the METH-induced memory disturbance and neuro-toxicity.

The present report is associated with some limitations such as the longer-term intervention is needed to illustrate more benefits or adverse effects of quetiapine. Also, we were not able to assess the craving in subjects with methamphetamine abuse under MMT. Thus, it seems that more assessment on craving caused by quitting is needed in further studies. In addition, a number of patients complained of quetiapine side effects, such as headache, vertigo and drowsiness, which this should be considered in the interpretation of our findings.

## 5. Conclusions

Finally, we found that administration quetiapine for 8 weeks in patients with MA and opioid co-abuse under MMT improved BDI, PSQI, IGT, FAS, DGSP-Reverse, yet did not affect BAI, TMT subscales, and DGSP-Straight. Further evidence are needed to show the relative impact of quetiapine on MA and opioid co- abuse under MMT and perhaps larger samples should be used. The combination therapy of quetiapine and methadone in opioid withdrawal protocols could be also introduced for increasing the quality of life and decrease the risk of MA abuse.

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## Authors' contributions

NSJ and HRB contributed in conception, design, statistical analysis, drafting of the manuscript and supervised the study. NSJ, AGh, FSGH, MS and HRB contributed in data collection and manuscript drafting.

## Conflicts of interest

None.

## Clinical trial registration number

[www.irct.ir:IRCT20171106037290N1](http://www.irct.ir:IRCT20171106037290N1).

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jad.2019.03.078](https://doi.org/10.1016/j.jad.2019.03.078).

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