

# Research Paper: The Effects of Quetiapine on Craving and Withdrawal Symptoms in Methamphetamine Abuse: A Randomized, Double-Blind, Placebo-Controlled Trial



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## ABSTRACT

**Background:** Patients with Methamphetamine Abuse (MA) are susceptible to many complications like craving, and withdrawal symptoms. These trials were designed to evaluate the effect of quetiapine administration on craving and withdrawal symptoms in MA abuse.

**Methods:** This trial was conducted on 60 people with MA abuse to receive either 100 mg quetiapine (n=30), or placebo (n=30) every day for 2 months. The Desire for Drug Questionnaire (DDQ) and Amphetamine Withdrawal Questionnaire (AWQ) scores were evaluated at baseline and after 2 months' intervention. For data analysis, t test, and the Chi-square test were applied in SPSS v. 18.

**Results:** Quetiapine significantly decreased DDQ (P=0.002) and AWQ symptoms (P=0.001) compared to the placebo. Furthermore, there was a significant difference among groups in terms of the frequency of negative urine tests (P<0.001).

**Conclusion:** This trial showed that administration of quetiapine supplements for 2 months in individuals with MA abuse had beneficial effects on craving and withdrawal syndrome.

## 1. Introduction:

Methamphetamine (MA) abuse is one of the crucial health problems in the world [1]. For the first time, in 2005, MA and its effects had been reported from Southeast Asia [2]. MA has been found an important health problem and the MA depen-

dence is approximately 1% among Iranian [2-4]. New insights into this condition indicated that a variety of actions could be related to reducing MA abuse. Methadone Maintenance Treatment (MMT) programs can be introduced as an effective action which enables to enhance the quality of life or social functioning [5]. Despite several implementations of the MMT, some challenges, and barriers have remained. Many evidence reports re-

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vealed that the prevalence of MA is increasing in MMT programs [3, 6, 7]. MA abuses are linked to many psychiatric impacts (e.g., increase craving, and withdrawal syndrome) [8, 9].

Pharmacotherapy has emerged as a new venue in the reduction of substance abuse. Despite the many benefits of these therapies, there are different challenges for the utilization of pharmacotherapy agents in the treatment of drug abuse. The pharmacological impact of antipsychotic agents for drug abuse therapy has been documented in psychotic disorder subjects [10]. Quetiapine is a pharmacological agent which is known as an atypical antipsychotic drug. It could be employed for treating different disorders such as cognitive disturbance in chronic schizophrenia [11]. Much evidence documented that quetiapine could be used for decreasing alcohol craving and withdrawal symptoms [10].

Previous reports indicated that quetiapine is associated with the ameliorated impacts on clinical symptoms. Current evidence indicated that quetiapine administration at a dosage of 100 mg/d for 2 months ameliorate psychiatric symptoms e.g., cognitive and mental health disorder [12]. Sattar et al. [10] demonstrated that using an average of 153 mg/d quetiapine for 1 month in subjects with coexisting substance abuse disturbance show favorable impacts on the craving scale. Furthermore, some evidence revealed that administration of quetiapine dosage of 50-100 mg/d, for 3 months to individuals with cocaine dependence, and bipolar disorder show pharmacological impacts on cocaine cravings [13].

Quetiapine could decrease the dopamine blockade, which may result in a reduction in substance abuse. Moreover, quetiapine enables to inhibits the dopamine receptors in the limbic system, which be associated with minimal blockade of dopamine in the reward process [10, 11]. To the best of our knowledge, the evidence on the impacts of quetiapine on clinical symptoms in MA abuses is little. So, we aimed in this trial to evaluate the effects of quetiapine on craving and withdrawal symptoms in MA abuse.

## 2. Materials and Methods

### Study design

This randomized, double-blinded, placebo-controlled trial was registered on the Iranian website (<http://www.irct.ir: IRCT20171106037290N1>), the Primary Registry in the World Health Organization (WHO) Registry Network set up in collaboration with the Ministry of Medi-

cal and Health Education. This trial was conducted on 60 MA abusers under MMT, aged 18-65 years who were referred to the Golabchi Clinic (KAUMS clinic center). The study protocol was approved by the Research Ethics Committee of Kashan University of Medical Sciences (KAUMS). All informed consent forms were reviewed by the Research Ethics Committee of KAUMS. The inclusion criteria were aged 18 to 65 years, under MMT, MA abuser, seeking treatment for MA abuse, as assessed by DSM-IV, at least weekly MA use during a preceding three months. Also, the exclusion criteria were psychotic symptoms, suicide, cocaine, and alcohol dependence, cardiovascular disturbance, recent use of over-the-counter or prescription drugs that would be expected to have major interaction with quetiapine, metabolic diseases (e.g., epilepsy, diabetes, and neurological).

### Study protocol

Patients were randomized into two groups and supplemented with either 100 mg quetiapine or placebo (n=30), every day for 2 months. We have used the mentioned dose of quetiapine based on a past study in individuals with liver diseases, bipolar disorder, and cocaine dependence [13, 14]. All individuals completed three physical activity and 3-day food records as metabolic equivalents [15] at weeks 0, 2, 4, 6, and 8 of the treatment. Quetiapine and placebo tablets were prepared in the same way. They had an identical shape, color, size, odor, and texture. The tablets were packed in the same container with a code number. The tablets were prepared by a pharmacist of Zahravi, Tabriz City, Iran. Thus, participants, physician, and other investigators were all blind to the treatment group assignments. The randomization was conducted using computer-generated random numbers. Allocation and randomization were concealed from the patients and researchers until the completion of the final analyses.

### Study measurements

#### Clinical measures

Craving: The original Desire for Drug Questionnaires (DDQ) such as 13 questions for three main craving components, desire, and intention to drug use, negative reinforcement, and control. High validity and reliability of the DDQ have been reported for the evaluation of periodic and instant cravings in Iran. The DDQ has a good level of internal consistency (Cronbach alpha =0.89) [16].

### Withdrawal symptoms

The Amphetamine Withdrawal Questionnaire (AWQ) is a short, valid, and reliable measure for assessing amphetamine withdrawal scales. The items were rated as follows: 1. Not at all; 2. Very little; 3. A little; 4. Quite a lot; 5. Very much [17]. The possible range of scores is 0–40 with a higher score indicating greater severity. The high validity of the AWQ for questions individually and the whole questionnaire was 80% and 86.5%. The internal consistency (Cronbach alpha) was 0.84 for the whole questionnaire [18].

### Sample size

To evaluate the sample size, we used a clinical trial sample size formula where type I ( $\alpha$ ), and type II errors ( $\beta$ ) were 0.05 and 0.20 (power=80%), respectively. Based on a prior study [19], we used a Standard Deviation (SD) of 8.9 and a change in the mean of 5.1 days, considering DDQ as the main variable. The calculation showed that 25 patients should have been enrolled in each group. Assuming a dropout of 20% patients in each group, the final sample size was determined to be 30 patients per each group.

### Statistical analysis

To test the normality of variables, the Kolmogorov-Smirnov test was used. Dietary characteristics, an-

**Table 1.** General characteristics of the study participants (n=28)

Variable	No. (%) / Mean±SD		P2
	Placebo Group	Quetiapine Group	
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
Use of other drugs (%)			
None	23 (82.2)	19 (67.8)	
Sedative-Hypnotic	2 (7.1)	5 (17.9)	0.40†
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/wk)	0.59±0.4	0.47±0.4	0.29
Frequency of MA use (wk)	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

Obtained from the independent t test;

† Obtained from the Pearson Chi-square tes;

MA: Methamphetamine; MMT: Methadone Maintenance Treatment; BMI: Body Mass Index.

**Table 2.** The effect of Quetiapine on craving and withdrawal symptoms in methadone maintenance treatment patients (n=28)

Variables	Mean±SD						P2
	Placebo Group			Quetiapine Group			
	Baseline	Week 8	Change	Baseline	Week 8	Change	
DDQ	41.6±8.5	40.7±8.3	-0.89±3.4	40.5±8.6	35.3±7.1	-5.14±6.8	0.002
AWQ	36.3±6.9	37.0±6.3	0.67±2.7	35.9±6.1	33.0±6.0	-2.96±4.0	0.001

2. Obtained from the independent t test.

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AWQ: Amphetamine Withdrawal Questionnaire; DDQ: Desire for Drug Questionnaire.

thropometric, study outcomes, and of the intervention groups were compared using the independent sample t test. Also, qualitative data were analyzed using the Chi-square test. The data were presented as the mean differences with 95% confidence intervals. The P values of less than 0.05 were considered statistically significant. All statistical analyses were done with SPSS version 18.

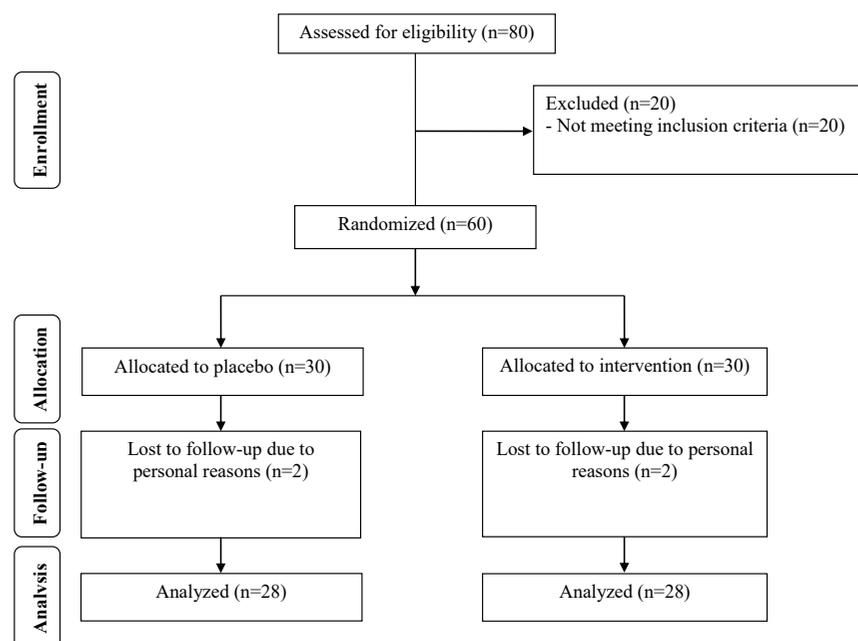
### 3. Results

Two participants in the supplemented group and 2 in the placebo group left the study for personal reasons (Figure 1). No serious side effects were reported following the consumption of quetiapine in MA abuse patients under MMT. Though grade 1 side effects were reported in 7 patients in the quetiapine group (daytime sleepiness

(n=3), headache (n=3), and dizziness (n=1)), nobody was excluded from the trial.

There was no significant difference among the two groups in terms of height, weight, age, BMI, frequency of MA use, duration of MA use, the dose of MA use, age of MA experience, duration of methadone use, and methadone dose (Table 1).

Quetiapine was significantly decreased DDQ score (P=0.002) and AWQ score (P=0.001) (Table 2). Besides, there was a significant difference between the two groups in terms of the frequency of negative urine tests in the treatment group (P<0.001). Also, in this study, B=1.28 (e B=e1.28=3.5). In other words, patients in the treatment group are 3.5 times more likely to have a negative urine test than the control group (Figure 2). Changes in DDQ

**Figure 1.** Summary of study patients' selection

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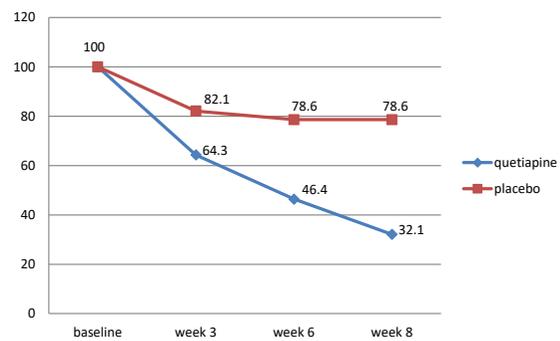
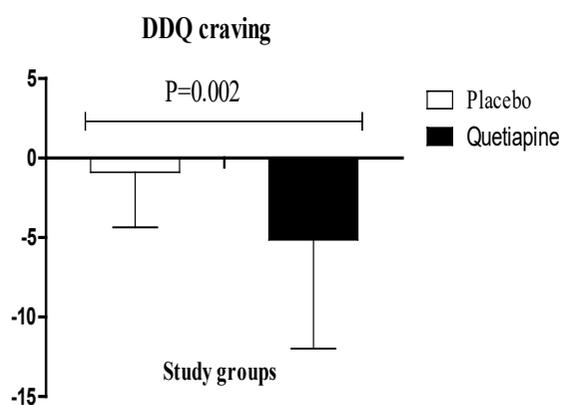
and AWQ score in patients MA abuse under MMT receiving quetiapine and placebo are presented in Figure 3.

#### 4. Discussion

In our study, we observed the effects of quetiapine intake on craving and withdrawal symptoms after 8 weeks of supplementation in cases with MA abuse. Our report indicated that receiving quetiapine for 2 months by subjects with MA abuse who were under MMT, in comparison to the control group, decreased craving and withdrawal signs. For the first time, this report assessed the impacts of quetiapine on craving and withdrawal signs of subjects with MA abuse who were under MMT.

MA abuse is related to various problems such as craving and withdrawal syndrome [8, 20]. Many studies proposed the benefits of new antipsychotic drugs in decreasing drug abuse-related disorders in cases with a dual diagnosis [21, 22]. In a study, Brown et al. [13] revealed that administration of quetiapine could significantly enhance the psychiatric signs and cravings dosage of 50-100 mg/d for 3 months. Another reports, showed that administration of 50-300 mg/day quetiapine (average 153 mg/day) for 28 day to in patients with substance dependence disorders was beneficial for the treatment of craving scale and withdrawal symptoms [10].

Rizkallah et al. [19] observed that administration of quetiapine was related to a better craving score. Moreover, various reports proposed an anti-craving impact

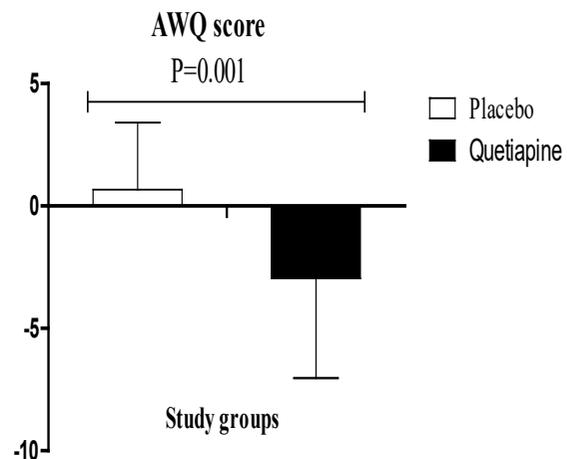


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Figure 2. The effect of quetiapine on urinary test methamphetamine

of quetiapine in psycho-stimulants and alcohol [23, 24]. Although, the high dopamine receptor binding of anti-psychotics could be related to the aggravation in craving in the subjects with methamphetamine abuse [25, 26]. Some reasons for discrepant results may be various study designs, lack of observing baseline values of dependent variables as well as characteristics of study individuals, various dosages of quetiapine administration also the duration of the study. It is well found that quetiapine exerts its addictive effects via the limbic system's reward process, possibly mediated by the release of the neurotransmitter dopamine [27].

Pharmacological agents that block dopamine could inhibit this process, possibly resulting in attempts to counter this blockade via elevating MA abuse. This could be



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Figure 3. Means±SD changes in DDQ and AWQ score in patients with MA abuse under MMT receiving quetiapine and placebo

P value was obtained from the independent t test; n=28 in each group.

MMT: Methadone Maintenance Treatment; DDQ: Desire for Drug Questionnaire; AWQ: Amphetamine Withdrawal Questionnaire

explained by the enhanced substance use observed after therapy with typical antipsychotic agents, which block dopamine D2 receptors. Moreover, new antipsychotics, such as quetiapine, show significantly lower dopamine blockade, which cannot result in any elevation in MA use. Quetiapine enables to transiently block the dopamine receptors in the limbic system, which could contribute to a minimal blockade of dopamine in the rewarding process [28]. However, there may also be some other processes that lead quetiapine to reduce MA use. The serotonergic neurotransmission might show one of these processes [29].

We did not evaluate the effects of quetiapine administration on serum and urinary quetiapine. The longer-term intervention may indicate more benefits or side effects of quetiapine. Furthermore, we could not evaluate the pain in individuals with MA abuse. So, it seems that more assessment of pain caused by quitting is needed in further studies.

## 5. Conclusions

We showed that taking quetiapine for 2 months by MA abusers improved withdrawal and craving symptoms. The combination therapy of quetiapine with MMT programs could be introduced to decrease withdrawal syndrome and craving in patients under MMT.

## Ethical Considerations

### Compliance with ethical guidelines

This randomized, double-blinded, placebo-controlled trial was registered on the Iranian website (<http://www.irct.ir>: IRCT20171106037290N1), the Primary Registry in the World Health Organization (WHO) Registry Network set up in collaboration with the Ministry of Medical and Health Education. The study protocol was approved by the Research Ethics Committee of Kashan University of Medical Sciences (KAUMS). All informed consent forms were reviewed by the Research Ethics Committee of KAUMS.

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### Author's contributions

All authors contributed in preparing this article.

### Conflict of interest

The authors declared no conflict of interest.

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