Effects of Dextromethorphan on reducing methadone dosage in opium addicts undergoing methadone maintenance therapy: A double blind randomized clinical trial

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Abstract

BACKGROUND:

Dextromethorphan (DM) is an N-methyl-D-aspartate (NMDA) receptor antagonist that may be useful during opiate addiction process, especially in reducing methadone consumption in methadone maintenance therapy (MMT). The goal of the current study was to evaluate the effects of oral administration of DM on reducing methadone dose in MMT used to treat illicit opioid drug abuse.

METHODS:

A double-blinded randomized clinical trial was designed. Seventy two opiate abusers undergoing MMT were randomly divided into two groups. Participants in the intervention group were medicated by DM while those in the control group received placebo. After a 6-week follow-up, methadone consumption dosage, quality of life (QOL) and withdrawal symptoms were assessed and compared between the two groups by repeated measure ANOVA statistical test.

RESULTS:

The mean of methadone consumption in the DM and control groups were 62.7 mg/day (52.7-72.7) and 70.4 mg/day (60.4-80.4), respectively. No statistically significant difference was found between the two groups among the four evaluations made (F = 1.192, P = 0.279). There were not any significant differences in withdrawal symptoms between the two groups (P > 0.05). Total mean scores of QOL in the intervention and control groups were 84.8 (78.7-90.8) and 77.8 (71.8-83.7) (P > 0.05), respectively.

CONCLUSIONS:

Although DM might be useful for opioid dependence treatment, results of the current study did not reveal any statistically significant differences. Therefore, further studies exploring this possibility are needed.

KEYWORDS: Methadone, Dextromethorphan, Opiate Dependence, Addiction, Maintenance Therapy

Methadone is a synthetic opioid with long acting effect which is frequently administrated to treat acute opioid withdrawal symptoms. Methadone maintenance therapy (MMT) is one of the most common methods of long-term treatment of illicit opioid abuse.[1] MMT has been customary in Iran for treatment of opioid addiction. A systematic review of randomized controlled trials has shown that higher methadone doses were more effective than doses under 60 mg in both retention on maintenance treatment and reduction of illicit drug use.[2] However, parallel to treatment with methadone, another phenomenon named tolerance is acting. In many cases, tolerance is induced during MMT and methadone dosage consumption enhances.[1,3,4] Although it was supposed that negative auto-regulation was responsible for tolerance

creation, the activation of N-methyl-D-aspartate (NMDA) receptors has been proved to have an essential role in opioid tolerance. NMDA receptor antagonists have the ability to inhibit the development of opiate tolerance and dependence.[5–7] In addition, NMDA receptor antagonists can indeed inhibit tolerance to different mu opioids.[5,7]

Many studies demonstrated that the combination of an NMDA-receptor antagonist and morphine decrease analgesic tolerance of morphine.[5,7–9]

Some NMDA-receptor antagonists like dextromethorphan (DM) have been used for tolerance reduction in MMT.[10] However, few studies investigated DM usage in lack of tolerance to methadone during MMT. Therefore, there is a need to further explore the effects of NMDA receptor antagonists on the development of tolerance and sensitization to opiates. The aim of the current study was to evaluate the effect of oral administration of DM for reducing methadone dose in MMT of illicit opioid abuse. Additionally, we compared the side effects of DM and assessed patients' quality of life.

Methods

Design: A double blind randomized controlled clinical trial was conducted from January 2009 to January 2010. The study design is shown in Figure 1. The study was approved by Research Council and the Research Ethics Committee of Isfahan University of Medical Sciences (Research project number: 388046).

Inclusion criteria were

1- Opium addiction diagnosis based on DSM-IV criteria in the interview by psychiatrist;
2- Patient's age between 20-60 years;
3- Being a good candidate for MMT.

Exclusion criteria were:

1- Any medical problems including acute or chronic diseases;
2- Disturbance of liver function test;
3- Serum blood urea nitrogen (BUN) > 20 mg/dl or serum creatinine > 1.2 mg/dl;
4- Sensitivity to DM;
5- Abuse of other drugs like hallucinational agent, crack, and etc.

Participant recruitment: All participants were selected from substance abuse clinic at Noor hospital associated with Isfahan University of Medical Sciences. Sample size was calculated based on two mean comparison formula and 95% confidence and 80% power. The effect size was considered based on the range of methadone consumption between 30 to 120 mg. Overall, 72 patients with opium addiction were included and divided into two groups of 36. A researcher conducted the eligibility check using the abovementioned criteria and explained what would happen in the two arms of the trial and the randomization process. After the researcher summarized the information in the participant information sheet and responded to the questions about the study, the participants provided written consents. Then, participants were randomly allocated into two arms by a computer software. Every patient took a 4-digit code. Finally, EPI-6 software was used to randomly allocate the subjects into two groups of intervention and control. Only the main researcher knew about the code of allocated individuals. Evaluations were done by another investigator who was blinded regarding the allocation.

Procedure: In the beginning, all participants underwent laboratory liver function, serum BUN and creatinine tests to check liver and renal function. After randomization, the first group received 60 mg DM daily for 4 days. Then, the dose was increased to 120 mg daily (60mg/12h) for 4 days. In the third 4-day period, DM dosage was increased to 240 mg daily (120mg/12h) which continued through the next 6 weeks. However, in the other group (considered as control), the subjects were receiving placebo using the same process in the intervention group. DM and placebo were both made by School of Pharmacy at Isfahan University of Medical Sciences.

Measurements: The World Health Organization Quality of Life questionnaire (WHOQOLQ) and Short Opioid Withdrawal Scale (SOWS) were completed for each participant by a trained staff member. WHOQOLQ is a valid questionnaire to evaluate quality of life (QOL) designed by the World Health Organization (WHO). Nedjat et al. have also validated this questionnaire for Iranian population.[11] SOWS is a scoring system for evaluating the frequency and severity of withdrawal symptoms in patients recruited in opioid rehabilitation programs. It has been designed by Handelsman et al. in 1987.[12] This questionnaire was adapted for Iranian patients and has been applied in several studies.[13–15] The average methadone consumption was registered by the researchers in data sheets. First evaluation was done at the onset of the study to provide baseline data. Second evaluations were done every two weeks until 6 weeks after the study was started.

Statistical analysis: Statistical analysis was performed using SPSS for Windows (ver.17; SPSS Inc., Chicago, IL, USA). Comparisons between the groups were made by t-test for means and chi-square test for nominal variables. Repeated measure of analysis of variance (ANOVA) was used to evaluate changes of methadone consumption and QOL scores during 6 weeks. Variance homogeneity, as a presumption of repeated measure ANOVA, was tested by Mauchly's test. Levene's test was also used to investigate homogeneity of variance in both DM and control groups. Friedman test was used for repeated measurement of nominal variables such as changes of withdrawal symptoms during the 6-week assessment in each group. The changes of each withdrawal symptom were evaluated between the two groups using Fisher's exact test.

Results

Seventy two patients completed all the follow-up stages of this study. All participants were male. The range of age was 20-52 years (mean = 31.2 ± 7). Table 1 shows demographic characteristics of participants in the two groups. As shown, no significant differences were found between the intervention and placebo groups.

The mean of methadone consumption during follow-up is demonstrated in Figure 2. Totally, the mean of methadone consumption in DM and control groups were 62.7 mg/day (95% CI of mean: 52.7-72.7) and 70.4 mg/day (95% CI of mean: 60.4-80.4), respectively. There were not any significant differences between the two groups regarding methadone dosage. Repeated measure of ANOVA did not show any statistically significant difference between the two groups among the four evaluations made (F = 1.192; P = 0.279).

After 6 weeks of fallow-up, the difference of SOWS scores was not significant between the DM and placebo groups (F = 2.98; P = 0.09). The mean SOWS scores for each group were 9.2 (95% CI of mean: 6.8-11.5) vs. 12.1 (95% CI of mean: 9.7-14.4), respectively. Table 2 shows the frequency of withdrawal symptoms in participants. The most frequent symptom was yawning in both groups. There were no significant differences between the two groups regarding any of the withdrawal symptoms (Fisher's exact test P > 0.05). The changes in withdrawal symptoms during the 6-week follow-up were checked in every group by Friedman test. There was not any significant difference in symptoms during 6 weeks in each group.

Assessment of QOL declared the mean scores of QOL during the 6 weeks of follow-up to be higher in the intervention group. Total mean score of QOL in the intervention and control groups were 84.8 (95% CI of mean: 78.7-90.8) and 77.8 (95% CI of mean: 71.8-83.7), respectively. Neither the difference between QOL scores in the intervention and control groups (F = 2.671; P = 0.107) nor the trend of QOL during 6 weeks (F = 1.566; P = 0.2) were statistically significant in the two groups (Figure 3).

Discussion

Findings of the present study showed the combination of methadone and DM not to statistically decrease dose of methadone consumption in MMT program participants. Likewise, statistically significant differences were not observed in the QOL between the two groups.

DM and methadone are NMDA receptor antagonists.[6] DM may represent as an adjuvant medication in methadone replacement therapy. It is broadly involved in opiate-induced plasticity, including the development of methadone tolerance and sensitization.[5,8] The inclusion of low-dose DM to methadone might be beneficial for the reduction of methadone dosage during MMT.[2,8,16,17]

In the current study, the maximum dose of DM was 240 mg daily and the follow-up period lasted for 6 weeks. In contrast to our findings, Cornish et al. found a significant relation between methadone reduction dosage and DM medication. However, they had prescribed 480 mg DM daily and followed the patients for only two weeks. Like our study, they could not find a significant difference between the placebo and DM groups.[10]

We also analyzed the QOL and found that subjects in the DM group had higher QOL than those in the control group, though the difference was not statistically significant.

There were many advantages in this study. First, with the exact quality control, the study benefitted from a high-quality methodology. In addition, the appropriate sample size, which was estimated by exact statistical formula, increased the power of the study to detect small differences between the groups. Finally, it should be noted that statistical multivariate tests were considered significant if type I error was less than 0.05 (α < 0.05).

At the end, although DM might be useful for opioid dependence treatment due to its effects in improving opiate tolerance,

reducing withdrawal symptoms experienced during detoxification, and inhibiting conditioned reactions to drug-related stimuli (which play an important role in drug seeking and relapse following treatment),[10] our study could not demonstrate this effect. Therefore, further studies investigating this possibility are needed.

On the other hand, there were some limitations in our study. We had some resource and time limitations to evaluate patients using other questionnaires including those assessing personality, mood, and mental status. While we administered low dose DM (240mg/d), another study administered it at 480 mg/d.[10] We tried to use homogenous administration of methadone and although the mean dosage of methadone differed in the two groups, it was not statistically significant.

Authors' Contributions

MS designed the study and drafted the manuscript. AZ collected samples and drafted, MAR analyzed the data and drafted the manuscript.

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Footnotes

**Conflict of Interests** Authors have no conflict of interests.

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Figures and Tables

Figure 1
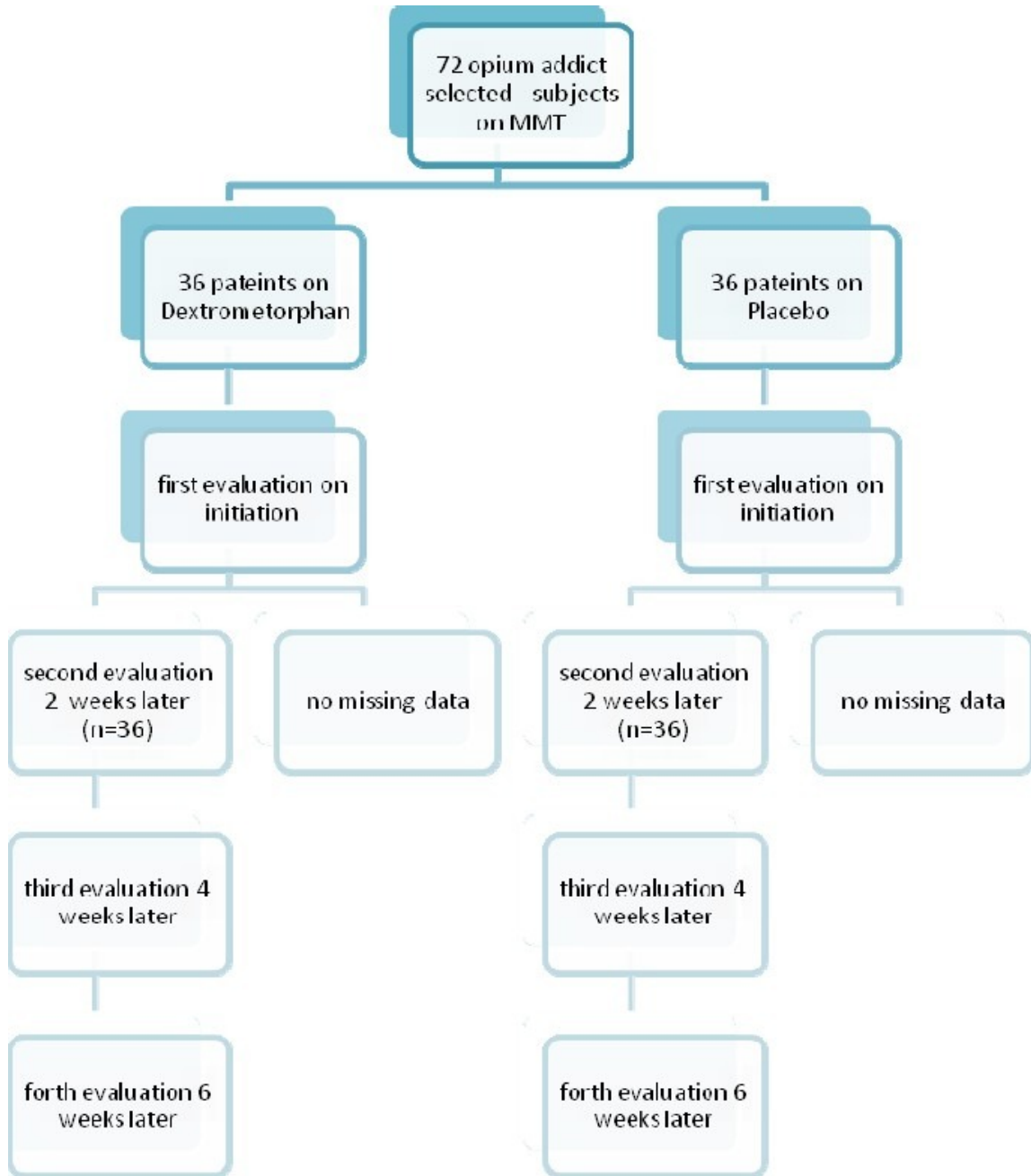
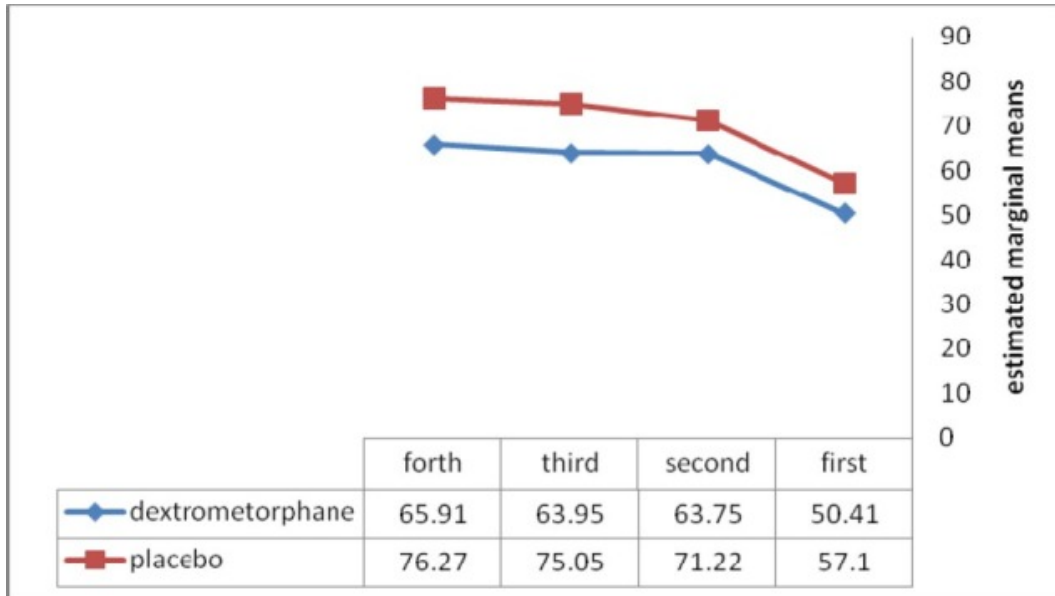Schematic diagram of the study process

Table 1

	Dextromethorphan	Placebo	P value
Age (mean ± SD)	31.6 ± 6.9	30.9 ± 7.2	NS*[†]
Education			
Illiterate	6	3	
Primary	14	13	NS*[‡]
High school diploma	13	20	
University graduate	3	0	
Marital status			
Single	19	19	NS*[¥]
Married	17	17	

*NS: Non significant, †: independent t-test, ‡: Pearson's chi-square test with Yate's correction, ¥: Fisher's exact test

Demographic characteristics of patients separated in two groups.

Figure 2

	forth	third	second	first
dextrometorphane	65.91	63.95	63.75	50.41
placebo	76.27	75.05	71.22	57.1

The mean of methadone consumption during the 6-week follow-up separated for the two groups.

Table 2

	Dextromethorphan				Placebo			
	First	Second	Third	Fourth	First	Second	Third	Fourth
Illness	21	20	23	18	20	22	22	16
Tenesmus	7	11	10	7	11	12	12	12
Rigidity	10	14	16	12	20	18	19	20
Cold sensation	18	15	15	11	22	21	19	20
Palpitation	12	14	13	7	15	9	14	14
Bodily pain	15	17	16	12	20	13	18	18
Yawning	23	22	23	22	27	22	17	23
Insomnia	13	12	11	6	17	15	11	17
Diarrhea	2	6	4	7	9	4	7	6
Depression	19	24	22	19	24	22	17	19
Anxiety	21	26	20	16	23	22	17	17
Agitation	19	24	23	16	22	22	18	21
Irritability	13	19	17	15	20	15	19	19
Desire to substance abuse	10	22	12	10	15	19	19	22

* Comparison of each symptom between the two groups was done by Fisher's exact test. Comparison between each measure in each group was done by Friedman test.

Frequency of opioid withdrawal symptoms during the 6-week follow-up[*].

Figure 3

	forth	third	second	first
dextrometorphane	83.72	84.08	84.86	86.53
placebo	76.08	76.22	77.67	81.17
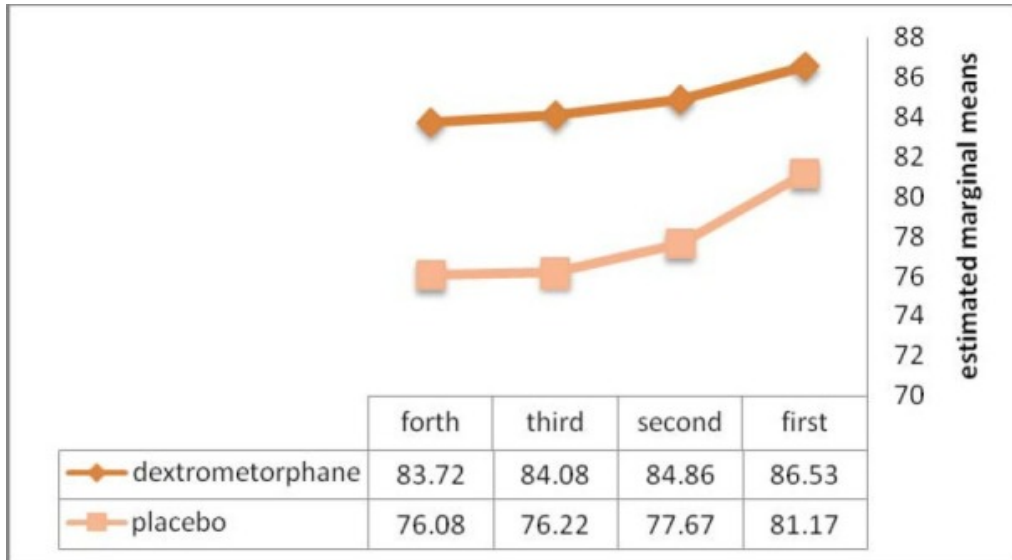
The mean of quality of life scores during 6 weeks of follow-up separated for the two groups.