

The effects of gabapentin on methadone based addiction treatment: A randomized controlled trial

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Abstract: Gabapentin is a potentially useful drug in alleviating the hyperexcitatory painful states in the control of opiate dependence in acute detoxification and the stabilization phase. This study aim was to evaluate the effectiveness of gabapentin adds-on methadone therapy on lowering the methadone. This randomized double blind controlled clinical trial conducted at an outpatient rehabilitation clinic. Sixty patients using opium, opium extract and heroin were randomly assigned to two groups (34 in treatment group and 26 in control group); one group was prescribed combination of methadone (40-120 mg) and gabapentin (300 mg) as group A, and the other group was given methadone (40-120) and placebo as group B. The subjects were followed up for three weeks after intervention. There were 60 outpatients including 51 males with the mean age of 40.9±9.2. Daily dose and cumulative dose of methadone during the treatment was found to be significantly higher in group B (73.8±19.5 mg daily vs. 58.9±11 mg daily and cumulatively 1550.7±409.7 mg vs. 238.3±238.2 mg, $p=0.001$). When the patients were stratified based on the kind of abused drug, the methadone dose was seen to be significantly reduced in the opium addicted patients in the group A. Group A showed more withdrawal symptoms whereas the most common complain of group B was sedation particularly during the first three days. The results showed that gabapentin is an effective adds-on therapy when is added to methadone. This drug leads to relief of withdrawal symptoms and lower methadone consumption.

Keywords: Gabapentin, Methadone, addiction.

INTRODUCTION

Discontinuing of opiates is accompanied by some symptoms including intense back and leg pain with restlessness (Goldstein, 1961). Methadone is widely used for detoxification and maintenance therapy of opioid addiction (Stotts *et al.*, 2009; Guo *et al.*, 2010).

Gabapentin is shown to be effective as for patients with drug-resistant partial seizures and it is also prescribed for neuropathic pain (Rosner *et al.*, 1996; Mellick and Mellick, 1997; Bonnet *et al.*, 1999; Rice and Maton, 2001), therefore it is a potentially useful drug in alleviating the hyperexcitatory painful states, as seen in opiate withdrawal. Gabapentin has been found as an effective therapy of alcohol and cocaine withdrawal (Myrick *et al.*, 2001; Kumar and Jain, 2003). This drug also has been used as an adjuvant in the control of opiate dependence in acute detoxification and the stabilization phase. (Martinez-Raga *et al.*, 2004; Kheirabadi *et al.*, 2008) Gabapentin with dose of 900mg per day could reduce the score of Subjective Opiate Withdrawal Scale (SOWS) during and after methadone assisted withdrawal (Freye *et al.*, 2004). Gabapentine, as prescribed for the treatment of neuropathic pain, has been reported to be effective in decreasing opioid-induced hyperalgesia in patients who are abstinent and stable in methadone treatment (Bisaga *et al.*, 2006). Acute detoxification

associated back pain; limb thrashing and a restless-leg-syndrome could be attenuated by this drug (Field *et al.*, 1997; Kheirabadi *et al.*, 2008).

Many problems related to standard withdrawal therapy have resulted to an increasing interest to develop some other strategies to reduce the complications. Tiagabine, gabapentin and transcutaneous electrical nerve stimulation in combination with methadone have been suggested to reduce these symptoms (Marson *et al.* 2000; Gonzalez *et al.*, 2007).

Gabapentin was reportedly an effective therapy for withdrawal associated symptoms in acute, middle time and chronic management with different identified dose. This study has been designed to evaluate the effectiveness of gabapentin adds-on methadone therapy on lowering the methadone usage dose and its side effects and also the symptoms of patient undergone out-patient treatment for opiate dependence.

METHODS

This was a randomized controlled double blind trial conducted at an out-patient rehabilitation clinic in Bojnurd, the capital of Northern Khorasan province (Iran). From all patients who had come to this center, 60 patients using opium, opium extract and heroin were involved to this study from August 2010 to February 2011. All the patients had to meet the Diagnostic and

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Statistical Manual of Mental Disorders IV (DSMIV) criteria for addiction. Opiates had to be used for at least 12 months and the consumption dose should not be changed during last month. They did not have to use other analgesics, opiates, psychoactive and illicit drugs within three weeks before investigation. Also they had not to have known psychological disorder, known methadone and gabapentine sensitivity. The known cases of medical or psychological disorders and pregnant or lactating women were not included to this study. The patients had to have Subjective Opiate Withdrawal Scale (SOWS) more than twelve. The subjects with positive urine morphine test after 10 days or lapse after the beginning of treatment and those who had developed toxicity symptoms of methadone (respiratory depression, bradycardia, QT prolongation and hallucination) were excluded from the study. Written consent was obtained from all subjects after detailed explanation. The study was approved by ethic committee of Mashhad University of Medical Sciences.

Patients were randomly assigned to two groups; one group was prescribed combination of methadone (40-120 mg) and gabapentine (300 mg) as group A, and the other group was given methadone (40-120) and placebo as group B. The randomization was performed by a randomization table. The evaluating physician and nurse and the patients were unaware of the drug packs, the gabapentine and placebo capsules were similar in shape. The subjects were followed up for three weeks after intervention. The gabapentine dose was elevated from 300mg daily at first day to 300 mg three times a day at third day and maintained until 21st day. The dose of methadone was administered for each patient based on the amount of last month use of abused drugs and was adjusted considering the withdrawal symptoms during first three days after cessation. The patients were questioned for drug abuse in each follow up visit.

STATISTICAL ANALYSIS

Student t-test was used to compare the quantitative variables. For comparison of the SOWS score between two groups Mann-Whitney U test was used. For

evaluating qualitative data chi square test was performed. P value less than 0.05 was considered significant. Summarized data are presented as mean± standard deviation. All analyses were done using SPSS V.16 software.

RESULTS

There were 60 out-patients including 51(85%) males with the mean age of 40.9±9.2 years (21-61 years) in this study who met DSM-IV criteria for opiate dependence. After randomization 34 patients were assigned to group A and 26 patients to group B. All patients completed the assigned treatment. There were non significant differences in mean age, gender, addiction duration, addiction drug and rout of abuse (nasal, oral or IV) between two groups (table 1).

Daily dose and cumulative dose of methadone during the treatment was found to be significantly higher in group B which took methadone and placebo (73.8±19.5 mg daily vs. 58.9±11 mg daily and cumulatively 1550.7±409.7 mg vs. 1238.3±238.2 mg, $p=0.001$) (fig. 1). When the patients were stratified based on the kind of abused drug, the methadone dose was seen to be significantly reduced in the opium addicted patients in the group A (table 2).

Observed side effects during the study were significantly different between two groups ($p<0.001$). Group A showed more withdrawal symptoms whereas the most common complain of group B was sedation particularly during the first three days (table 3).

DISCUSSION

Based on the results of the present study consumed methadone was significantly lower in the group treated by gabapentin in addition to methadone. This could be the result of higher severity of the withdrawal symptoms in the placebo group. The gabapentin group was shown to have more sedation than placebo group which had withdrawal symptoms (dysphoria, muscle spasm and twitching and irritability). These findings suggest gabapentin as an effective medication in the management

Table 1: baseline characteristics of patients

		Group A (n=34)	Group B (n=26)	p value
Age (mean±SD, years)		41.2±10.5	40.34±8.4	0.7
Gender (number, male)		30	21	0.328
addiction duration (mean±SD)		4.7±1.8	4.8±2.75	0.86
addiction drug	heroin	10	9	0.665
	Opium	17	10	
	opium extract	7	7	
Rout of administration (smoking/oral)		25/1	32/2	1

Note: Group A was treated with methadone and gabapentine; group B was treated with methadone and placebo.

Table 2: Comparison of methadone dose in different study groups

Addiction drug	Group	Mean $\pm$ SD	<i>p</i> value
Opium (total dose)	Group A (n=17)	1155 $\pm$ 185.6	0.15
	Group B (n=10)	1501 $\pm$ 411.3	
Opium extract (total dose)	Group A (n=7)	1380 $\pm$ 280.6	0.805
	Group B (n=7)	1500 $\pm$ 414.3	
Heroin (total dose)	Group A (n=10)	1281 $\pm$ 231.1	0.013
	Group B (n=9)	1645 $\pm$ 436	
Opium (daily dose)	Group A (n=17)	55 $\pm$ 8.83	0.15
	Group B (n=10)	71.5 $\pm$ 19.6	
Opium extract (daily dose)	Group A (n=7)	65.7 $\pm$ 13.3	0.805
	Group B (n=7)	71.4 $\pm$ 19.7	
Heroin (daily dose)	Group A (n=10)	61 $\pm$ 11	0.013
	Group B (n=9)	78.33 $\pm$ 20.8	

Note: The analyses were performed using Mann-Whitney U test; group A was treated with methadone and gabapentin; group B was treated with methadone and placebo.

Table 3: Side effects and symptoms in each group

Group	Side effect and symptoms			Total
	None	Sedation	Withdrawal syndrome	
Group A	19 (55%)	15 (45%)	0	34 (100%)
Group B	16 (61.5%)	0	10 (38.5%)	26 (100%)
Total	35 (58%)	15 (25%)	10 (16.6%)	60 (100%)

Data are represented as number (%)

Note: Group A was treated with methadone and gabapentine; Group B was treated with methadone and placebo. $P > 0$.

of withdrawal symptoms. Gabapentin affects by inhibiting voltage-gated Ca^{2+} -channels and increasing gamma-aminobutyric acid neurotransmission and modulating the excitatory amino acids at the N-methyl-D-aspartic acid reports (Brown *et al.*, 1996; Kelly *et al.*, 2011), which are increased during the withdrawal period.

Satisfaction plays an important role in determining retention to addiction (Compton *et al.*, 2010). Gabapentin has been reported by Freye *et al.* as an effective anti-hyperalgesic agent in rapid opiate detoxification (Field *et al.*, 1997) In a study on 26 patients (experimental: 10; placebo: 16) gabapentin (titrated to 2400). mg/day), as prescribed for the treatment of neuropathic pain, is effective in decreasing opioid-induced hyperalgesia in patients who are abstinent and stable in methadone treatment (Bisaga *et al.*, 2006). Martinez-Raga *et al.* reported that gabapentin, at a dose of 600 mg three times daily as an add-on medication to a standard detoxification regimen, decreased symptoms of heroin withdrawal and drugs used for management of the symptoms and in seven heroin dependent individuals (Kheirabadi *et al.*, 2008). But in a study by Kheirabadi *et al.* no difference was found in symptoms severity and methadone consumption dose between two groups. They explained their non significant results as a result of low dose of gabapentin or small sample size (Kheirabadi *et al.*, 2008). In other study by Bisaga *et al.* gabapentin 1600 mg bid was no more

effective than placebo in the treatment of cocaine dependence. It was shown to cause more side effects in cocaine dependence than placebo group. The most frequently reported adverse effects were dizziness (10% of gabapentin-treated patients versus 0% in placebo group) and tiredness/sedation (8% versus 4%). And some sporadic symptoms were constipation, indigestion, sore throat, insomnia, diarrhea and dysuria in 12% of the patients treated with gabapentin and 4% of the patients treated with placebo in cocaine consumer (Bisaga *et al.*, 2006). In a study on 76 patients gabapentin (2400 mg/day) showed poor treatment retention and no effect on cocaine abuse in comparison with tiagabine among methadone-stabilized cocaine abusers (Marson *et al.* 2000).

CONCLUSION

The results of the present study showed the gabapentin as an effective add-on therapy when is added to methadone. This drug leads to relief of withdrawal symptoms and lower methadone consumption.

Small sample size and short-term follow-up were limitations of this study. To more detailed evaluation of the effect of the gabapentin on the methadone dose reduction and withdrawal symptoms, patients should be evaluated for their symptom severity in further studies.

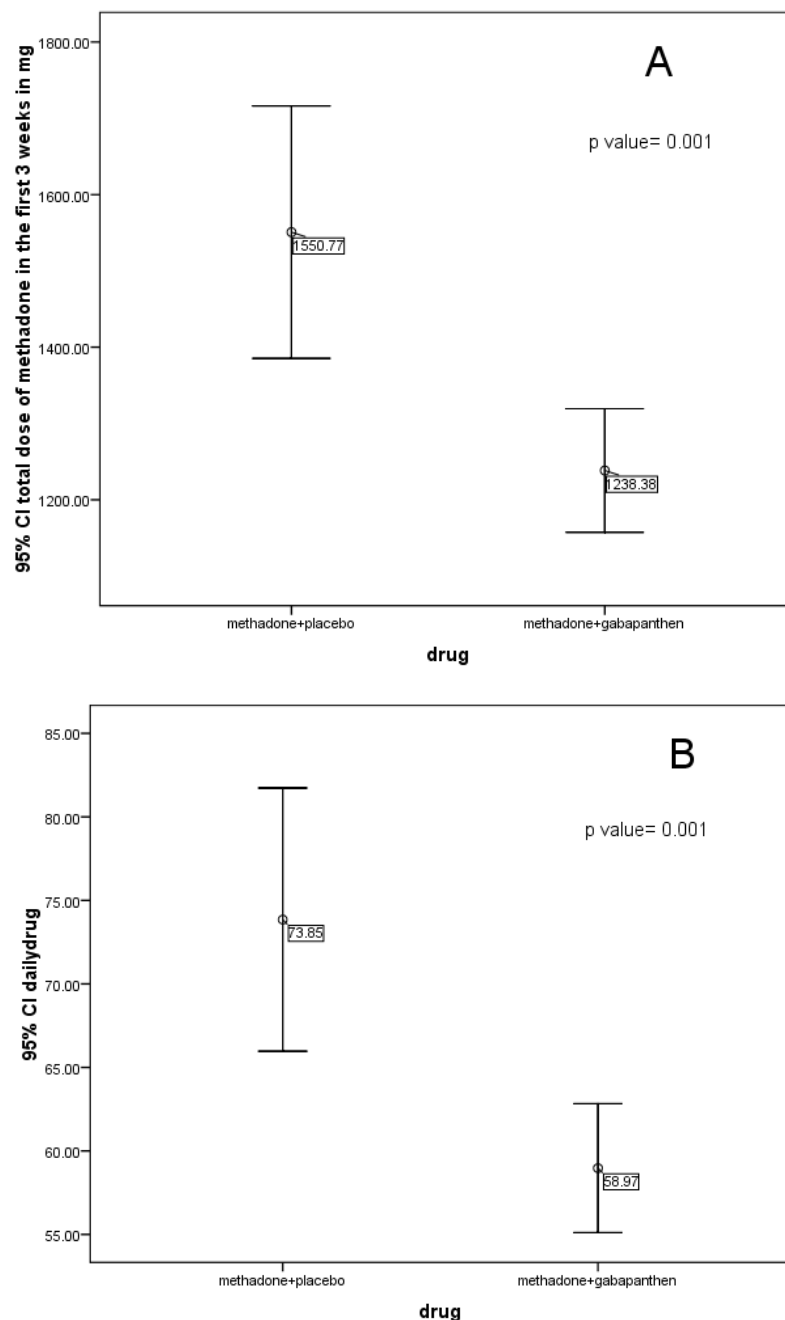


Fig. 1: Total (A) and daily (B) dose of methadone requirement and its 95% confidence interval in two study groups.

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