

# EFFICACY OF TOPIRAMATE AS AN ADJUNCT MEDICATION IN HEROIN WITHDRAWAL: A RANDOMIZED CONTROL TRIAL

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## ABSTRACT

**Objective:** To compare the efficacy of Topiramate in reducing Heroin withdrawal symptoms in Iranian patients.

**Design:** Double blind placebo-controlled trial.

**Place & Duration of Study:** Study was conducted in Ibn-e-Sina Hospital, Mashad, Iran in a period of two years i.e., 2006-07.

**Subjects & Methods:** The study was carried out on 149 patients with Heroin dependency (74 in Topiramate group and 75 in Treatment as usual group) using 2 standard questionnaires for assessment of withdrawal symptoms, Subjective opiate withdrawal scale (SOWS) and objective opiate withdrawal scale (OOWS). Information was analyzed by chi-square test for qualitative variables and T-test & Mann-Whitney for quantitative variables in SPSS software.

**Results:** 22 subjects were excluded from the study. Both groups had no significant differences in age, sex, education, number of previous withdrawal and past history of other drug use. Results indicated decrease in objective withdrawal symptom, significant in 3rd ( $p=0.000$ ), 5th ( $p=0.004$ ) and 7th ( $p=0.026$ ) day and subjective withdrawal symptom significant in 3rd ( $p=0.000$ ) day in topiramate group.

**Conclusions:** Our study showed that Topiramate can use for control of withdrawal symptom in patient with Heroin dependency.

**Key words:** Topiramate, Detoxification, Withdrawal, Opium, Heroin.

## INTRODUCTION

Opioid dependency is a maladaptive pattern of using opioids that besides its harmful personal effects, has many social adverse consequences such as unemployment, divorce, economic deprivation and illegal acts<sup>1</sup>. Therefore different specialists and especially psychiatrists have paid a considerable attention toward this problem.

Substance dependency includes behavioral (focusing on seeking behaviors and their related evidence) and somatic dependency (physiologic effects of repetitive pattern of substance use) and its treatment should be directed to these 2 dimensions.

Detoxification is considered as one important phase of substance dependency treatment. Many

patients delay substance abstinence because of their inability to tolerate the withdrawal symptoms. So clinicians try to safely ameliorate these symptoms<sup>2,3</sup>.

Patients who use the substances with short half lives such as Heroin<sup>4</sup> have more problems in the withdrawal of these opioids.

Noradrenergic neurons have an important role in causing withdrawal symptoms. Clonidine, an alpha 2 adrenergic agonist, is a common used drug for decreasing the noradrenergic hyperactivity and reducing these symptoms<sup>5</sup>. Clonidine is not an efficient drug in management of many symptoms such as anxiety, restlessness, muscular pain and craving<sup>6</sup>. Clonidine use also has been limited because of its side effects including hypotension and sedation in patients with acute cardiac disease and moderate to severe hypotension<sup>7</sup>.

Methadone, an opioid receptor agonist, could be used for reducing the withdrawal symptoms at tapered doses, but its most important problems include the long term treatment period and difficulties in providing Methadone<sup>8</sup>. Therefore, because of suboptimal efficacy of Clonidine and disliking the use of opioid agonists by some patients, many clinical trials were carried out to

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examine the efficacy of other drugs such as Nimodipine<sup>9</sup>, Mianserin<sup>10</sup> and Doxepine<sup>11</sup> in the opioid withdrawal phase.

With the recognition of kindling and its probable role in substance abuse<sup>12</sup> the importance of anticonvulsants in the treatment of substance dependency was revealed. Anticonvulsants have no dependency risk and are useful for the treatment of comorbid psychiatric disorders in these patients<sup>13</sup>. Efficacy of carbamazepine in detoxification of benzodiazepines, alcohol and opioids and in reducing cocaine consumption has been supported in some studies<sup>13</sup>. Valproate Na has been proposed as a treatment of alcohol withdrawal and reducing cocaine consumption, but it seems not to be effective in the treatment of benzodiazepine detoxification<sup>13</sup>.

Excitatory amino acid (EAA) antagonists inhibit the process of morphine tolerance and dependence<sup>14</sup> and Lamotrigine suppress the release of EAA with its effect on Na channels<sup>15</sup>. Some data show the efficacy of Lamotrigine in the opiate dependency<sup>16</sup>.

One study in 2004 assessed the efficacy of Gabapentine in the treatment of Heroin withdrawal in 7 outpatients. Results showed that it was effective in controlling the withdrawal symptoms. The limitations of this study were the small sample size and lack of structured scale for assessment of withdrawal symptoms<sup>17</sup>. Another study in 2004 indicated that adding carbamazepine –mianserin to usual medications was effective in reducing the opiate withdrawal symptoms<sup>18</sup>.

Topiramate is an antiepileptic drug that has been shown to be effective in opiate withdrawal treatment in a few researches, but these studies had small sample sizes and did not have an assessment scale for measuring the withdrawal symptoms. So, we decided to examine the efficacy of Topiramate in reducing Heroin withdrawal symptoms in Iranian patients.

## SUBJECTS AND METHODS

This was a double blind placebo-controlled trial that was carried out on 149 patients with Heroin dependency in Ibne –sina hospital–Mashhad in the period of 2 years (2006-2007).

The sample was selected from admitted patients with Heroin dependency for detoxification who had the inclusion criteria for the study and willingness to cooperate. Demographic characteristics, history of previous or current substance use and history of psychiatric and somatic disorders were collected through a semi-structured interview by a psychiatrist. Patients were randomly divided into Topiramate and placebo groups. In the First group, subjects received clonidine (0.2-0.8mg min o.6), Ibuprofen (1200-2400 mg min 1800), lorazepam (2-6 mg min 4), amitriptyline (25-75 mg min 50) and Topiramate with a starting dose of 75-100 mg that was added up to min 150-200 mg after 3 days and continued until the end of treatment. The placebo group took the same regimen without Topiramate that was replaced with a placebo in the same shape and color of Topiramate. During the 10 days of hospitalization, withdrawal

**Table 1**  
**Demographic data of patients referred for opiate detoxification**

Groups	Mean age	Sex ratio M/F	Job status		Marital status		
			Unemployed	Employed	Married	Single	Divorced
Topiramate	24.02	5.62	35	32	9	47	11
Placebo	23.78	7.53	36	24	16	36	8
	P=0.147 t=0.404	P=0.419 X2=0.654	P=0.379 X2=0.773		P=0.1172 X2=3.516		

**Table 2**  
**History of substance use in referred patients for detoxification**

Groups	Mean time of substance dependency	Ways of consumption			Number of abstinences		History of using other substances		
		Inh	Inj	Inh+inj	<3	>3	Al.*	H.	Op.
Topiramate	43.34 sd=21	51	8	8	56	11	16	13	25
Placebo	36.20 sd=18	42	12	6	45	15	14	12	24
	P=0.129 Z=-1.518	P=0.455 X2=1.576			P=0.231 X2=1.432		P=0.94 X2=0.0	P=0.92 X2=0.0	P=0.756 X2=0.090

Inh = Inhalation

Al=Alcohol

Inj=injection

H=Hashish

Op= Opioids

**Table 3**  
**SOWS in different days in Topiramate and placebo groups**

	SOWS1	SOWS3	SOWS5	SOWS7	SOWS10
z	-0.844	-4.358	-1.898	-0.429	-1.105
p	0.398	0.000	0.058	0.668	0.269
Mean score(Placebo)	54.15	53.75	37.25	25.63	20.17
Mean score(Topiramate)	54.67	52.22	35.82	25.34	20.18

**Table 4**  
**OOWS on different days in Topiramate and Placebo groups**

	OOWS1	OOWS3	OOWS5	OOWS7	OOWS10
z	-0.494	-4.407	-2.913	-2.220	-1.932
p	0.621	0.000	0.004	0.026	0.053
Mean score (Placebo)	10.82	10.87	6.40	5.00	4.12
Mean score (Topiramate)	10.37	10.31	5.88	4.85	4.00

symptoms of patients were assessed in days 1,3,5,7 and 10.

Data was collected using 2 standard questionnaires for assessment of withdrawal symptoms, Subjective opiate withdrawal scale (SOWS) and objective opiate withdrawal scale (OOWS).

OOWS is an objective measure for intensity of opiate withdrawal symptoms. This scale is one part of initial assessment and is also used for rating the response to medication in the treatment course. This questionnaire has 13 questions which are graded as 0 (does not exist) or 1 (exist). So, the scores range between 0 to 13.

SOWS is a self-report scale which has 16 questions. These questions are graded in a likert scale from 0 (does not exist) to 4 (severe). The scores range between 0 to 64. This questionnaire indicates the severity of withdrawal symptoms graded by the patient.

These scales have repeatedly been used in the different studies for assessment of withdrawal symptoms<sup>19-22</sup>. Side effects of medications in 2 groups were assessed by a psychiatrist.

Collected data were described by descriptive statistics and then were analyzed using the chi-square and t- test in the SPSS -11/5.

## RESULTS

Among the 149 patients 74 were in the Topiramate group and 75 were in the placebo group. Twenty-two patients 15 from placebo group and 7 from Topiramate group dropped –out during 10 days of study. Twenty patients did not tolerate the withdrawal symptoms and 2 subjects had psychosis.

Finally 127 patients completed the trial (60 in placebo group and 67 in the Topiramate group). There were not significant differences between 2 groups in terms of mean age ( $p=0.147$ ), sex distribution ( $p= 0.419$ ), employment status ( $p= 0.379$ ) and marriage ( $p=0.127$ ). Results have been showed in table 1. Also 2 groups did not have significant differences in terms of the length of Heroin dependency ( $p=0.129$ ), the way of Heroin consumption in one year before the study ( $p=0.455$ ), history of using alcohol ( $p=0.942$ ), hashish ( $p=0.933$ ) and other opiates except Heroin ( $p=0.756$ ) (table 2).

Mann-whitney test showed a significant difference between 2 groups in terms of Subjective symptoms of opioid withdrawal in SOWS. Patients in Topiramate group had less subjective symptoms on third day of detoxification compared to placebo group ( $P=0.000, Z=-4.358$ ) (table 3). Based on Mann-whitney test there was a significant difference in 2 groups in objective symptoms of opioid withdrawal. These symptoms were less in Topiramate group than placebo group on days 3( $P=0.000, Z=-4.407$ ), 5( $P=0.000, Z=-2.913$ ) and 7 ( $P=0.026, Z=-2.220$ ) (table 4).

The most common side effects of medication in both groups were speech difficulties (6 patients in placebo and 7 in Topiramate group) and Ataxia (2 in placebo and 9 in Topiramate group). Frequency of ataxia was significantly higher in patients receiving Topiramate compared to placebo group ( $P=0.021, \chi^2=2.185$ ).

## DISCUSSION

Neurophysiology of opioid withdrawal symptoms has not been recognized completely.

There are some neurotransmitter systems like noradrenergic, colinergic, dopaminergic and glutaminergic

that have been proposed to be important in withdrawal symptoms of opioids.

The glutaminergic projection from paragigantocellularis to locus coeruleus (LC) activates the LC noradrenergic cells that is related to symptoms of opioid withdrawal. N-Methyl-D-aspartic acid (NMDA) and Alpha – amino-3 hydroxy-5- methyl-4-isoxazole propionic acid (AMPA) receptors are important in this activation, but the role of AMPA is more important than the other one<sup>23</sup>. Topiramate with inhibition of AMPA receptors reduces the activation of LC<sup>24</sup> without any effect on NMDA receptors. It does not have PCP –like effects and seems to be an appropriate choice for alleviating opiate withdrawal symptoms. There are 2 studies in this area. The first one was mainly a case report that reported the efficacy of Topiramate in treating opiate withdrawal. In this study Topiramate was introduced at a dose of 500 mg/day and tapered to 100 mg/day on day 5 for 3 patients and was efficacious on more symptoms of the opiate withdrawal<sup>25</sup>. The second research in 2004 compared the withdrawal symptoms in 3 groups of 10 patients with opiate dependency receiving Topiramate, Carbamazepine/ Mianserin and Clonidine respectively. The results indicated that patients in Topiramate group needed less adjunctive medications like analgetics and muscular for their withdrawal symptoms. The authors concluded that Topiramate is a valuable drug for opiate detoxification<sup>26</sup>.

In the present study we had a large sample size in contrast to 2 previous researches in 2002 (on 3 patients) and 2004 (on 30 patients), so the results are more reliable. The starting dose of Topiramate in our study was 75-100mg/day that is more appropriate for patients' compliance compared to the initiating dose of 500 mg/day in the research in 2002.

In this study we used 2 scales (SOWS and OOWS) for evaluating the subjective and objective withdrawal symptoms of opioids. With more robust methodology, we found a significant difference in 2 groups in objective symptoms of opioid withdrawal. These symptoms were less in Topiramate group than placebo group on days 3 ( $P=0.000, Z=-4.407$ ), 5 ( $P=0.000, Z=-2.913$ ) and 7 ( $P=0.026, Z=-2.220$ ). A significant difference was seen between 2 groups in terms of Subjective symptoms of opioid withdrawal in SOWS. Patients in Topiramate group had less subjective symptoms on third day of detoxification compared to placebo group ( $P=0.000, Z=-4.358$ ). Because the most withdrawal symptoms of Heroin is seen in first 24-48 hours of withdrawal, the efficacy of Topiramate on third day seems to be more important.

Limitations of the present study include: examining the inpatients only, not using Topiramate alone and also higher doses of Topiramate (for example, 500 mg/day) for withdrawal symptoms. Further researches need to be done on use of Topiramate alone, in comparison to other treatments for detoxification.

In conclusion, our study indicated that Topiramate added to usual treatment of opiate withdrawal is more efficacious than the usual treatment alone.

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