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Comparison of the effect of naltrexone with or without fluoxetine for preventing relapse to opioid addiction

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Abstract

Introduction: Regarding the probable effectiveness of adding fluoxetine to a medical regimen of opioid treatment, the present study aimed to compare the effect of naltrexone with or without fluoxetine to prevent relapse to opioid addiction.

Materials and Methods: In this cross-sectional study in 2016, 93 people with an opium addiction who were detoxified in Imam Reza Hospital in Mashhad, Iran, were selected using a purposeful sampling method. They were randomly divided into two groups (naltrexone and naltrexone + fluoxetine). The morphine urine test was performed at the end of the 1st month, 2nd month, 3rd month, 4th month, and more than 4 months after detoxification. The data were analyzed through descriptive statistics, Fisher's exact test, Pearson chi-square, Independent samples t-test, Mann-Whitney test, and SPSS software.

Results: Finally, 73 patients (39 patients in the naltrexone group and 34 patients in the naltrexone + fluoxetine group) were evaluated. The two groups had no significant demographic variable differences except marital status. The findings showed no significant difference in the relapse rate between the two groups, although a lower rate of relapse was seen in the naltrexone + fluoxetine group than in the naltrexone group (P= 0.563). At the same time, the naltrexone + fluoxetine group had more positive morphine urine tests in the early months than the naltrexone group significantly (P= 0.040).

Conclusion: The present study showed that adding fluoxetine to naltrexone reduces the relapse rate, while it is associated with a shorter duration of retention than the naltrexone group.

Keywords: Addiction, Fluoxetine, Naltrexone, Opioid, Relapse

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Introduction

Opioid addiction is a chronic condition and a major health issue in the world (1). The high prevalence of opioid addiction in Iran, like other countries, leads to a heavy burden on the community (2). Opioid addiction is related to the high prevalence of negative consequences and an increased rate of morbidity and mortality (3-5). Based on the studies, more than 80% of opioid addicts had a relapse to substance abuse 6 months after quitting (6). Cessation or reduced doses of opioids in dependent individuals lead to uncomfortable physical and psychological symptoms called withdrawal syndrome, which continues for more than 14 days (7). So, management of opioid use treatment is an important challenge for health practitioners to use proper pharmacological treatment to reduce the risk of relapse in opioid addict individuals (8,9).

Naltrexone (NTX) is one of the pharmacological medications applied in opioid use disorder or alcohol use disorder. Naltrexone is a long-acting opioid antagonist that blocks μ-opioid receptors. An oral dose of naltrexone (50 mg per day) can block the effects of 25 mg IV heroin for 24 hours (10). A major part of patients with opioid use disorder accept NTX as a treatment to prevent relapse of opioid use (11,12). However, there is evidence that using NTX alone to prevent relapse of opioid use is not acceptable for all patients, and there are controversies about single-medication therapy with NTX (13,14). This issue encourages practitioners to use adjunctive pharmacological agents such as bupropion or Selective Serotonin Reuptake Inhibitors (SSRIs) to reduce the risk of relapse in dependent-opioid patients (15,16).

Fluoxetine is one of the marked SSRIs, which is used to treat major depressive disorder, anxiety disorders, and obsessive-compulsive disorders (17-19). Some studies suggest the effectiveness of fluoxetine combined with naltrexone in opioid addiction treatment, but there is a gap in clinical evidence, especially in Iran (20,21). So, the present study aimed to compare the effect of naltrexone with or without fluoxetine to prevent relapse to opioid addiction.

Materials and Methods

In this cross-sectional study in 2016, 93 people with an opium addiction who were detoxified in the special clinic of Imam Reza Hospital (AS) in Mashhad, Iran, were selected through the purposeful sampling method. They were randomly divided into two groups. The first group was treated with naltrexone, the second group was treated with naltrexone + fluoxetine for 4 months.

A general physician clinically examined the participants to rule out physical disorders, completed the questionnaire, and explained to the patient how to participate in the project and the side effects of the drugs. For the final evaluation, a psychiatric interview was conducted to confirm psychiatric conditions for entering the plan.

Inclusion criteria included age above 18 years, absence of psychiatric disorder or mental retardation based on clinical and family interview, absence of physical disorder based on physician's examination, completing the detoxification period and having a negative morphine urine test, willingness to participate, and not using illegal addictive non-narcotic compounds. The exclusion criteria included lack of cooperation in taking medicine, intolerance to medical therapy, not doing the morphine test, the necessity of taking medications that interact with fluoxetine or naltrexone, such as medications that are bound to proteins in large amounts, such as warfarin, and the occurrence of acute hepatitis during treatment with naltrexone. The first group with naltrexone (with the generic name naltrexone and product of Iran Daru company), which starts with a dose of 25 mg and reaches 50 mg once a day, and the second group with naltrexone + fluoxetine (with the generic name fluoxetine product of Dr. Abidi company) were treated with a daily dose of 20 mg up to a maximum of 40 mg in one daily session for 4 months. A toxicologist performed naltrexone therapy. The morphine urine test was performed after the end of the 1st, 2nd, 3rd and 4th month after detoxification during treatment with nurse supervision. All patients received the necessary treatments, including painkillers and related measures such as counseling in the same way and according to their needs.

Research instruments

A) The Demographic Checklist: It includes demographic variables such as age, gender, marital status, occupational status, educational level, and history of major physical or psychiatric illness.

B) The Morphine Urine Test: We conducted this test to assess the relapse of opioid use.

We analyzed the data through descriptive statistics, Fisher's exact test, Pearson Chi-square, Independent samples t-test, Mann-Whitney test, and SPSS software.

Results

This study was conducted on 93 patients (44 patients in the naltrexone group and 49 patients in the naltrexone + fluoxetine group).

Among these, 20 patients did not return for follow-up, and finally, 73 patients (39 patients in the naltrexone group and 34 patients in the naltrexone + fluoxetine group) were evaluated.

Table 1 presents demographic variables in two groups.

There were no significant differences between the two groups in demographic variables. Only marital status was significantly different between the two groups (*P*= 0.002).

Table 1. The demographic variables in two groups of opioid addicts

Variable	Naltrexone group Number (Percentage)	Naltrexone + Fluoxetine group Number (Percentage)	P (Test)
Gender			1.000 (Fisher's Exact test (2-sided))
Male	37 (94.9%)	32 (94.1%)	
Female	2 (5.1%)	2 (5.9%)	
Age (Year)	31.10 ± 9.51	32.30 ± 9.09	0.605 (Independent samples t-test)
Marital status			0.002(Pearson chi-square)
Married	24 (61.5%)	26 (76.4%)	
Single	15 (38.5%)	8 (23.6%)	
Occupational status			0.299 (Pearson chi-square)
Occupied	20 (51.3%)	23 (67.6%)	
Jobless	19 (48.7%)	11 (32.3%)	
Educational level			0.763(Mann-Whitney)
Elementary	14 (35.9%)	11 (32.4%)	
Middle to high school	10 (25.6%)	12 (35.3%)	
Diploma	11 (28.2%)	10 (29.4%)	
Higher education	4 (10.3%)	1 (2.9%)	

In terms of relapse rate, 21 patients (53.8%) and 16 patients (47.1%) in the naltrexone group and naltrexone + fluoxetine group had relapse, respectively. There was no significant difference in the relapse rate in the two groups (*P*= 0.563), although a lower relapse rate was seen in the naltrexone + fluoxetine group. The mean duration of relapse in the naltrexone group and the naltrexone + fluoxetine group was 3.4 ± 2.4 months and 2.0 ± 1.87 months, respectively.

The duration time of relapse was shorter in the naltrexone + fluoxetine group than in the naltrexone group (*P*= 0.040). Table 2 compares the mean duration time of relapse (positive urine test) in two groups.

Table 2. Comparison of the mean duration time of relapse (positive urine test) in five follow-ups in two groups

Group	End of 1st month	End of 2nd month	End of 3rd month	End of 4th month	> 4 months
Naltrexone group Number (Percentage)	7 (33.3%)	3 (14.3%)	2 (9.5%)	3 (14.3%)	6 (28.6%)
Naltrexone + Fluoxetine group Number (Percentage)	10 (62.5%)	3 (18.8%)	1 (6.3%)	0 (0.0%)	2 (12.5%)
Result of comparison ((Mann-Whitney test)	P= 0.049				

The results of Table 2 showed that patients in the naltrexone group had more positive morphine urine tests in the last months compared to patients in the naltrexone + fluoxetine group, while positive morphine urine tests were seen in the early months (end of the first and second months) in the naltrexone + fluoxetine group. The comparison results showed that the difference between the two groups was significant (P= 0.049).Investigating the relapse rate according to age group (< 40 years and ≥ 40 years), gender, and educational level (under diploma and diploma or higher education) in the naltrexone group and naltrexone + fluoxetine group indicated no significant differences in relapse rate according to gender, age group, and educational level in both groups (P> 0.05).

Discussion

This cross-sectional study compared the effect of naltrexone with or without fluoxetine to prevent relapse to opioid addiction. We evaluated 39 patients in the naltrexone group and 34 patients in the naltrexone + fluoxetine group. The findings showed no significant difference in the relapse rate in the two groups. However, a lower rate of relapse was seen in the naltrexone + fluoxetine group than in the naltrexone group. Although, the naltrexone + fluoxetine group had significantly more positive morphine urine tests in the early months (end of the first and second months) compared to the naltrexone group.In this line, Krupitskiĭ et al. in 2010 assessed the effect of naltrexone and fluoxetine in preventing relapse in 280 people with a heroin addiction. These patients were divided into four groups: naltrexone 50 mg/day + fluoxetine 20 mg/day (N/F), naltrexone + fluoxetine placebo (N/FP), naltrexone placebo + fluoxetine (NP/F), and naltrexone placebo + fluoxetine placebo (NP/FP). The results indicated that 43% of the N/F group, 36% of the N/FP group, 21% of the NP/F group, and 10% of the NP/FP group were in remission. Naltrexone with fluoxetine had a greater effect than naltrexone alone, especially in women. This effectiveness may be related to the presence of depression and anxiety in women (22). These findings are in line with our findings regarding the effectiveness of adding fluoxetine to naltrexone in treating opioid addiction. Although we evaluated a smaller sample size, and we had no placebo groups. Also, Krupitskiĭ et al. did not compare the time of relapse in patients. Another study conducted by Winstanley et al. assessed the effectiveness of fluoxetine added to voucher incentives in cocaine dependence among 145 patients undergone methadone maintenance treatment. The patients were divided into fluoxetine + voucher incentives (FV), fluoxetine placebo + voucher incentives (PV), fluoxetine alone (F), and fluoxetine placebo alone (P). The results revealed that the fluoxetine placebo + voucher incentives group had the longest treatment retention, and adding fluoxetine was not effective in preventing cocaine use in these patients (23). The results of this study were different from our findings. This difference may be related to a different substance (cocaine versus opioids). The present study had some limitations, such as a small sample size, limited to one geographical region, lack of assessing subclinical levels of depression or anxiety in opioid patients, and limited female patients compared to male patients. We suggest that future studies conducted on female addict patients and the psychological conditions of patients will be assessed more carefully through standard tools added to clinical interviews.

Conclusion

The present study showed that adding fluoxetine to naltrexone reduces the relapse rate, but there was no significant difference between the two groups. Also, the naltrexone + fluoxetine group had more positive morphine urine tests in the early months (end of the first and second months) than the naltrexone group.

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Conflict of Interests

The authors declare no conflict of interest.

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Ethical Considerations

The patients participated voluntarily, and all of them wrote the consent forms. This study was approved by ethical committee of Mashhad University of Medical Sciences.

Code of Ethics

IR.MUMS.REC.1389.74

Authors' Contribution

Azadeh soltanifar and Arezou Ashari wrote the manuscript, Azadeh soltanifar and Arezou Ashari performed the statistical analysis and validation, and both researchers approved the final article.

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