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Naltrexone Implant Treatment for Opioid Use Disorder: Analysis of Demographic and Clinical Data

Opioid Kullanım Bozukluğunda Naltrekson İmplant Tedavisi: Demografik ve Klinik Verilerin Analizi

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Abstract

Objective: The aim of this study is to evaluate the demographic and clinical features and outcomes of patients with opioid use disorder who underwent subcutaneous naltrexone implantation.
Method: A total of 51 patients with opioid use disorder admitted to Alcohol and Drug Addiction Research, Treatment and Education Center (AMATEM) of Van Training and Research Hospital and treated with naltrexone implant (1000 mg/3 month) were evaluated retrospectively. A data form for demographic and clinical features was filled based on medical records.
Results: The mean age of patients was 28.27±7.35 years, age of onset for any drug was 18.69±4.91 and 20.48±4.48 years for opioids. The most used first drug was cannabis followed by heroin. Majority of patients used heroin by smoking and inhalation. The laboratory test results were found to be within normal range. One patient was seropositive for HCV with normal liver function tests. 58.8 % of patients admitted for follow-up at least once in three months and 83.3 % of them maintained to be drug-free as revealed by urine toxicology tests. Local adverse reactions were most reported side effects due to naltrexone implant.
Conclusion: Naltrexone implant seems to be an effective and safe treatment choice in opioid use disorder as it increases treatment adherence and rates of drug-free urine samples, and is related with few adverse effects.

Keywords: Opioid use disorder, treatment, naltrexone implant

Öz

Amaç: Bu çalışmanın amacı, subkutan naltrekson implant ile tedavi edilen opioid kullanım bozukluğu tanılı hastaların demografik ve klinik özellikleri ile hastalık seyrini değerlendirmektir.
Yöntem: Van Eğitim ve Araştırma Hastanesi Alkol ve Madde Bağımlılığı Araştırma, Tedavi ve Eğitim Merkezi'ne (AMATEM) başvuran ve naltrekson implant (1000 mg/3 ay) ile tedavi edilen toplam 51 opioid kullanım bozukluğu olan hasta retrospektif olarak değerlendirildi. Demografik ve klinik veri formu tıbbi kayıtlar esas alınarak dolduruldu.
Bulgular: Hastaların yaş ortalaması 28.27±7.35 yıl, herhangi bir maddeye ve opioidlere başlama yaşı sırasıyla 18.69±4.91 ve 20.48±4.48 yıldı. En sık kullanılan ilk madde esrar ve onu takiben eroindi. Hastaların çoğunluğu eroini çekme ve soluma yoluyla kullanıyordu. Laboratuvar test sonuçları normal aralıkta bulundu. HCV için seropozitif bir hastanın karaciğer fonksiyon testleri normaldi. Hastaların % 58.8'i üç ayda en az bir kez izlem amaçlı başvurdu ve bunların % 83.3'ünün idrar toksikoloji testlerinde idrarda madde metobolitine rastlanmadı. Naltrekson implant tedavisi ile en sık lokal yan etkiler bildirildi.
Sonuç: Tedavi uyumu ve madde negatif idrar testleri oranını arttıran ve az sayıda yan etkiyle ilişkilendirilen naltrekson implant opioid kullanım bozukluğunda etkin ve güvenilir bir tedavi seçeneği gibi görünmektedir.

Anahtar kelimeler: Opioid kullanım bozukluğu, tedavi, naltrekson implant

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Introduction

Opioid use disorder (OUD) is a relapsing, lifelong brain disease leading to clinically significant impairment or distress and is characterized by loss of control of drug taking and persistent drug use despite the presence of adverse consequences (1,2). Because of conceptual problems between abuse and dependence, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) combined both as OUD and classified OUD under the title of "Substance-Related and Addictive Disorders" (1). OUD is defined as repeated opioid use within 12 months leading to functional impairment or distress with 2 or more of the diagnostic criteria including tolerance, withdrawal symptoms and craving (1). OUD is listed in mental, behavioral or neurodevelopmental disorders, as disorders due to opioid use in ICD 11 (International Classification of Disease 11) and is characterized by the pattern and consequences of opioid use (3).

The availability and use of illicit opioids and opioid-related deaths continue to rise all over the world (4). OUD is the main cause of admission to outpatient and inpatient addiction treatment clinics in Turkey and has been associated with 27.2 % of drug related deaths in 2022 (5). Treatment for OUD has been associated with improvement in clinical outcomes as patients under treatment are reported to be at lower risk for drug overdose, relapses and overall mortality (6,7). Medication indicated for the treatment of OUD includes buprenorphine (often combined with naloxone), methadone, and naltrexone (6,7).

Naltrexone is an opioid antagonist used in alcohol and opioid use disorder. Its effectiveness in stimulant use disorder is being researched and is also used in poly-drug use especially in patients using opioids and amphetamines (7). Naltrexone works by binding and antagonizing opioid receptors and blocking the physiological effects of opioids. Naltrexone prevents relapses and opioid intoxication and also has a favorable side effect profile (7). Naltrexone treatment can be initiated only when opioid withdrawal symptoms have subsided (8,9). The length of this time depends on the duration of use, type and amount of opioid and is at least seven days. Naltrexone is available as an oral tablet, an intramuscular depot injection and long-acting sustained-release implantable form (8,9). Long-acting forms are reported to be more effective in maintaining abstinence from opioids, because of high rates of non-compliance in patients with OUD (10). Also, poor outcomes in OUD patients treated with naltrexone have been related with short treatment time (6,7).

Long-acting, sustained-release naltrexone implant has been reported to be an efficient, safe and tolerable treatment choice in OUD and found to be superior to oral naltrexone in reducing opioid use, craving and hospitalizations, treatment compliance, time in treatment and abstinence rates (6,10). The aim of this study was to assess sociodemographic and clinical characteristics of patients with OUD who underwent subcutaneous long-acting sustained-release naltrexone implantation and determine the treatment response and effectiveness of naltrexone implant, the adverse reactions, treatment compliance and drug free time of the patients retrospectively to contribute the limited literature in this under-researched area.

Method

Study Settings and Subjects

Ethical approval was obtained from Van Training and Research Hospital Ethics Committee (dated 01/11/2018 and numbered 2018/15). The study was conducted in accordance with the criteria of the 2013 Helsinki Declaration. The study was designed as a retrospective descriptive study. A total of 51 patients who have been diagnosed with OUD (hospitalized with ICD 10 codes F11.1 and F11.2) according to DSM 5 and admitted to Alcohol and Drug Addiction Research, Treatment and Education Center (AMATEM) of Van Training and Research Hospital between January 2018 and December 2018 were evaluated. AMATEM is a health institution provides treatment for adult patients with drug and alcohol addiction, thus our sample group consisted of patients aged 18 and over. At the time study conducted, naltrexone implant was on the list of medicines supplied from abroad with health insurance for the patients with alcohol or opioid use disorder. Since the study planned to review a three-month follow up (as long as the duration of action of naltrexone implant), application of the first naltrexone implant was evaluated for each patient. One patient

used methadone before implantation and because of severe withdrawal symptoms developed, he removed his implant himself. The patient was informed and naltrexone implant were applicated again after follow-up and the patient were included in the study only with his second implant exceptionally. The patients with alcohol use disorder and underwent naltrexone implantation excluded.

Procedure

The study is a retrospective trial aimed to assess patients with OUD and who underwent subcutaneous naltrexone implantation. Patient examination, follow-up and reviewing past medical records were made by the same psychiatrist (Dr. Keskin). Patients firstly apply to outpatient clinic and provide a urine sample for drug urine test in AMATEM. After the initial evaluation which includes anamnesis, physical and mental examination, patients are evaluated with the results of drug urine test. Urine samples were analyzed by cloned enzyme donor immunoassay technique. Patients who diagnosed as OUD are taken into the outpatient or inpatient treatment program. After detoxification, maintenance treatment is continued with proper dose of buprenorphine+naloxone replacement therapy or antagonist therapy with naltrexone implant. At the time the study conducted oral naltrexone was not available in our country. The type of treatment (outpatient or inpatient, agonist or antagonist treatment) is determined based on patient's clinical, psychological and social status, past treatment attempts, additional medical diseases and patient preference. Naltrexone implant is contraindicated in acute hepatitis or liver failure, in ongoing opioid use and withdrawal symptoms, in patients have a positive urine screen for opioids and exhibited hypersensitivity to naltrexone before (8). Naltrexone also should be administered with caution to patients with thrombocytopenia or any coagulation disorder (8). Due to the contraindications and cautions blood tests and drug urine test were taken from all patients routinely.

A demographic and clinical data form consisted of the demographic characteristics (age, gender, employment, marital and educational status, place of residence, history of being in prison), clinical features (drug firstly used, drugs used lifetime, age of onset, using pattern, smoking etc.), detailed medical history (additional physical disorders, medications used regularly, past treatments for dependence), laboratory findings and outpatient follow-up data was filled based on medical records of hospital information management system.

Blood of patients for routine tests (complete blood count, blood biochemistry, serologic tests) was taken by staff of hospital blood draw unit and by clinical nurse for inpatients. Blood was taken in accordance with standard operating procedures of laboratory. HBsAg, anti-HBs, anti-HCV and anti-HIV tests were analyzed by Enzyme-Linked Immunosorbent Assay (ELISA) technique. If the laboratory test were normal and the drug urine test is negative for drugs, there was no contraindication for treatment and no symptom of withdrawal from opioids, patients were consulted to general surgery after written consent was obtained.

A small incision (2-3 cm) was made in the lower abdomen after a local anesthetic injection to numb the area. Naltrexone implant (1000 mg/3 month) was administered subcutaneously to all patients. The recommended treatment duration was at least one year, in other words at least four implants applied consecutively. Also, it was suggested all patients to apply for a follow-up examination to general surgeon and psychiatrist one week after implantation to assess implant site and adverse reactions and then, although it might vary from patient to patient, control examination was planned to be at least once a month.

Urine specimens were routinely screened to detect illicit substances and all patients were questioned for adverse reactions in admissions within three months and later.

Statistical analysis

The data was evaluated with the SPSS for Windows 21.0 statistical package program. Descriptive statistical analyses were carried out for the evaluation of the sample group. Frequencies and rates of categorical variables were determined. Categorical data was presented as frequencies and percentages, while numerical data was expressed as means and standard deviations.

Results

The mean age of 51 patients included in the study was 28.27±7.35 years. All patients were male and current cigarette smokers. The majority of sample group reported to be single or divorced, to have elementary or middle educational status and was unemployed. 5.9 % of patients had any age of physical illness and 23.5 % of them had been in prison at least once lifetime (Table 1).

Table 1. Socio-demographic and clinical characteristics of sample group

Variable	
Mean age (years) (mean ± SD)	28.27±7.35
Age of onset of using any substance	18.69±4.91
Age of onset of using opioids	20.48±4.48
Gender	N (%)
Male	51(100)
Marital status	
Married	15 (29.4)
Single/divorced	36 (70.6)
Education	
Elementary/middle school	35 (68.6)
Higher education	16 (31.4)
Employment	
Employed	18 (35.3)
Unemployed	33 (64.7)
Place of residence	
County	8 (15.7)
Others	43 (84.3)
History of being in prison	12 (23.5)
Cigarette consumption	51 (100)
History of physical disorders	3 (5.9)
The initial substance used	
Heroin	18 (35.3)
Cannabis	25 (49.0)
Others	8 (15.7)
Polydrug use lifetime	39 (76.4)
Method of heroin use (current)	
Smoking and inhalation	47 (92.2)
Snorting	1 (1.9)
Injection	3 (5.9)
History of treatment	
In an outpatient clinic	12 (23.5)
In an inpatient clinic	32 (62.7)
Using heroin with injection lifetime	8 (15.7)
History of substitution therapy with buprenorphine	37 (72.5)
History of treatment with naltrexone	10 (19.6)
Using any medication regularly	7 (13.7)

*SD: Standard deviation

When clinical features of patients were examined; average onset was found to be 18.69±4.91 for any drug and 20.48±4.48 for opioids. The most common used first drug was cannabis followed by heroin. Majority of patients used heroin by smoking and inhalation. Using heroin by injection was 15.7 % lifetime and 5.9 % currently. Majority of sample group underwent treatment in an inpatient and / or outpatient clinic before and used buprenorphine at the rate of 72.5 % and naltrexone at the rate of 19.6 %. The detailed socio-demographic and clinical features of sample group are presented in Table 1.

Table 2. Laboratory findings of sample group

Serologic tests	**N (%)**
Anti-HBs Positive	18 (35.3)
HBs-Ag Positive	0 (0)
Anti-HBC IgG Positive	4 (7.8)
Anti-HCV Positive	1 (2)
Anti-HIV Positive	0 (0)
Blood test results	(mean ± SD) (minimum-maximum)
ALT (alanine aminotransferase) (U/L)	20.18±8.47 (8-119)
GGT (gamma glutamyl transferase) (U/L)	17±9.13 (6-65)
Fasting Blood Sugar (mg/dL)	91±13.2 (68-114)
BUN (blood urea nitrogen) (mg/dL)	26.2±6.4 (8-38)
Creatinine (mg/dL)	0.7±0.13 (0.47-1.13)
Hemoglobin (g/dL)	12..3±14.1 (10.8-18.3)
PLT (Platelet) (10^3/µL)	262±60.8 (154-433)
WBC (White blood cells) (10^3/µL)	8.6±1.85 (4.15-12.76)

*SD: Standard deviation

Table 3. Urine toxicology test results of sample group

First Admission	**N (%)**
Opiates positive	48 (94.1)
Other drug (amphetamines, THC* etc.) positive	29 (56.9)
After application of naltrexone implant	
No follow up and drug urine test in 3 months	21 (41.1)
One follow-up and drug urine test in 3 months	23 (45.0)
Two follow ups and drug urine test in 3 months	3 (5.8)
Three follow up and drug urine test in 3 months	4 (7.8)
Drug urine test results (number of tests) **	41
Positive for only opiates	1 (2.4)
Positive for amphetamines and/or cannabis	3 (7.3)
Positive for both opiates and any other drug	1 (2.4)
Patients who had negative drug urine test for all drugs***	25 (83.3)
Patients who had negative drug urine test for opiates***	28 (93.3)

*THC: Tetrahydrocannabinol, one of the main active components found in marijuana

**The tests conducted in patients admitted to outpatient clinic after implant procedure at three-month follow-up

***Patients who admitted within three months after implantation and had at least one drug urine test (n=30)

Laboratory tests including hemogram, biochemistry and serological tests were conducted to exclude probable contraindications or risky situations. The test results were found to be within normal range. One patient was seropositive for HCV and anti-HBc IgG test of four patients was positive with normal liver function tests. In addition, all patients underwent drug urine testing before and after implant procedure. Before detoxification treatment drug urine test was positive for opiates in 94.1 % of patients and was positive for

other drugs especially for amphetamines at the rate of 56.9 %. It was observed 58.8 % of patients (n=30) admitted for control examination. Majority of these patients (83.3 %, n=25) were drug-free and 93.3 % of them (n=28) had negative drug urine test for opioids after naltrexone implant applicated. Table 2 presents the laboratory findings of sample group and the drug urine test results of patients are shown in Table 3.

The patients who admitted within in three months and / or later after implantation were evaluated for side effects of naltrexone implant. The most reported adverse reactions were site infection and local reactions including redness and itching which was seen at the rates of 37.5 % and 32.5 % respectively. 7.5 % of patients reported sleep disturbances and anxiety. Gastrointestinal system side effects like decreased appetite were seen 7.5 % of sample group. In only one patient the liver enzymes elevated after application of naltrexone implant. The adverse reactions to naltrexone implant are shown in Table 4.

Table 4. Adverse reactions reported after application of naltrexone implant

Adverse reaction reported	N* (%)
Decreased appetite	3(7.5)
Nausea and vomiting	1 (2.5)
Diarrhea	2 (5)
Elevation in liver enzymes	1 (2.5)
Headache	1 (2.5)
Fatigue	1 (2.5)
Sleep disturbances	3 (7.5)
Anxiety	3 (7.5)
Dysphoria	1 (2.5)
İtching	4 (10)
Redness	9 (22.5)
Pain in joints	1 (2.5)
Site infections	15 (37.5)

*N=40 (Patients who had follow-up and were questioned for side effects within 3 months or later

Discussion

Opioid use disorder is a growing and serious public health problem all over the world and the treatment options are limited due to local availability of opioid treatment programs, patient preference, effectiveness, and adverse effects (11). Naltrexone is the treatment of choice especially for patients who can't use opioid agonist treatment because of contraindications or prefer opioid free treatment, but utility of naltrexone is limited, primarily because of patient noncompliance with oral formulation (11,12). Sustained-release naltrexone implant may overcome this limitation and improve patient outcomes. In this study we present demographic and clinical features and outcomes of a patient group with OUD underwent naltrexone implant administration.

Although the drug use differs between genders by region and by drug type, using drugs remains to be more common among men than women all over the world (4). Our sample group was consisted of only male patients and this limits the generalizability of the study results. Absence of female patients may be associated with less frequent opioid use among woman, on the other hand this may be also a result of difficulties in accessing treatment, social consequences of opioid use, facing with greater stigma, unwillingness to receive treatment and treatment preference.

Treatment retention and staying sober are admitted as indicators of success in treatment for opioid use disorder by clinicians and patients and longer treatment time is associated with better clinical outcomes (13,14). Naltrexone implant is related with improvement in treatment compliance and the overall effectiveness of the treatment, as it has a long duration of effect and patients with naltrexone implant

decrease or quit heroin use and have more drug free urine tests (7-10) In a randomized, double-blind, double-placebo controlled trial comparing naltrexone implant with oral naltrexone, implant was shown to be superior to oral form in reducing relapse to regular heroin use, improving compliance rates and clinical outcomes and was not associated with major adverse events (10). In the literature; it is shown that naltrexone implant is efficient in preventing opioid overdose and reduction in the number of hospital presentations for physical as well as psychiatric reasons in patients with OUD (15-17). Concurrent with literature; we found that naltrexone implant was effective in increasing treatment adherence and rates of opioid-free urine samples as patients had at least one follow-up visit at the rate of 58.8 % and 83.3 % of these patients had drug free urine test. Also, urinalysis results were negative for opiates at the 93.3 % of patients tested and no patient presented with opioid overdose within three months.

Naltrexone can cause side effects like headache, anxiety, nervousness, difficulty in sleeping, low energy, joint and muscle pain, abdominal cramps, and nausea and vomiting in more than 10 % and loss of appetite, constipation, diarrhea, increased energy, increased thirst, feeling down, dizziness, irritability, delayed ejaculation, skin rash, and chills in less than 10 % of patients (8). It is reported that wound infections and / or local irritation due to naltrexone implant resolved with antibiotic and antiallergy medication treatment in a randomized controlled study (13). In the present study; local adverse reactions like site infections, redness and itching at the implant site were the most reported side effects and all were temporary and disappeared approximately in two weeks with anti-biotherapy. Gastrointestinal side effects were also resolved in one to two weeks without additional medical treatment.

In a study comparing naltrexone implant with oral naltrexone and placebo, it was found that depression, anxiety, and anhedonia were elevated at baseline but resolved within the first 1-2 months and naltrexone implant is a safe treatment in affective reactions too (18). Three patients reported anxiety and one patient complained of feeling distress and none of them require any additional treatment in our sample group. Another three patients had insomnia and started to take mirtazapine or quetiapine in the follow-up visits. It is shown that naltrexone implant is also safe for liver (19). One patient presented with elevated liver enzymes (approximately five times the top reference limit) and the liver enzymes return to normal on their own within about one month. As a result, naltrexone seems to be safe and related with few adverse and serious effects in its implant form too.

Methamphetamine use is growing globally and among patients with OUD and seems to have negative impacts on medication receipt, retention in treatment and opioid abstinence during treatment (20). In a study conducted in Russia it is reported that naltrexone implant decrease heroin and amphetamine use and suggest that naltrexone implant can be effective in polydrug use (21). In our study one patient continue to use cannabis and three of patients remain to use methamphetmines after treatment. The rate of amphetamine positive drug urine test decrease particularly in patients have follow-up visits but because of small sample size it is difficult to generalize the results. Given the importance of the issue, the larger longitudinal studies are warranted.

There are limited studies on naltrexone implant in our country. In a similar study performed by Kulaksızoglu et al. it was reported that 58.47 % of the patients with OUD and treated with naltrexone implant came to their controls for 12 weeks, 89.8 % of patients who had controls were negative for opiates and there was no substance metabolite in 82.2 % of these patients in urine toxicology test for 12 weeks (22). Although the rate of applying controls in 12 weeks seems to be lower in our study, the negativity rates of urine toxicology for opiates and all substances are similar among the patients who continue their follow-up. The difference between the rate of controls may be the result of methodological differences as patients admitted at least once a month were defined to had regular controls in our study. In another study comparing the discontinuation of maintenance treatment in patients treated with buprenorphine-naloxone and naltrexone implant, no significant difference was found between the groups and the rate of treatment discontinuation was reported as 72% in a follow-up period of approximately 130 days (23). In the present study, we observed that the number of admissions for control was highest in the first month, and then the number of patients admitted decreased. This may indicate a change in residence, continuing treatment in another institution,

well-being, or ongoing substance use. Further longitudinal and comparative studies with larger sample groups are needed.

In conclusion, opioid use disorder is a growing public health problem worldwide. The number of patients seeking for treatment is increasing over years but many treatment options like methadone agonist treatment, injectable forms of naltrexone are still not accessible in our country. Despite several limitations like the small sample size, the sample consisting of only males, retrospective study design, the absence of a control group, lack of advanced statistics and power analysis may result with poor generalizability, the findings of the present study suggest that naltrexone implant is a safe and effective treatment option for eligible patients, improve medication compliance and can be treatment of choice especially in patients who can't use opioid agonist treatment and / or prefer opioid free treatment and / or have poor adherence with oral naltrexone. As it is not a usual treatment and there are limited treatment options available for patients with OUD, it is expected to contribute the scarce literature in this under-researched area, provide an insight for both the patients and the physicians who will administer the treatment and guide for further studies. Finally, it is clear that arrangements are needed in accessing of patients to treatment programs and medications for patients with opioid use disorder to ensure the remission, recovery, maintenance of their well-being and rehabilitation.

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