

Rate and Predictors of Severe Withdrawal Symptoms in an Accelerated Opioid Detoxification Program

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Abstract

Background: Opioid addicts usually quit treatment due to the severe withdrawal symptoms associated with it. Accelerated opioid detoxification programs were launched with the aim of making the detoxification process easier to complete for opioid patients and to improve compliance to the treatment. However, there is limited information on the prevalence of severe withdrawal symptoms and on the risk factors which may lead to such symptoms in accelerated opioid detoxification. The objective of this study, therefore, is to determine the frequency of severe withdrawal symptoms in accelerated detoxification programs and the factors responsible for this.

Methods: A total of 191 participants were included in the study. All the participants had been diagnosed with opioid addiction and admitted to Moodist Hospital, where they underwent the Accelerated Detoxification Program (ADP) between November 2018 - July 2019. A naltrexone implant was applied to the participants subsequent to the treatment. The Addiction Profile Index Clinic Form (API-CF) and the Clinical Opiate Withdrawal Symptoms Scale (COWS) were administered to participants during the study process.

Results: The Naltrexone implant was applied to all participants at the end of the detoxification treatment. It was found that 9.4% of the people in the ADP treatment process had severe withdrawal symptoms. Furthermore, the presence of severe withdrawal symptoms on the first day was seen to be a factor determining the severity of withdrawal symptoms in the following days. The mean COWS scores and standard deviation of the participants who experienced severe withdrawal symptoms subsequent to the first, second, third, fourth and fifth days of the treatment were 6.64 ± 2.53 , 5.47 ± 2.99 , 8.14 ± 5.51 , 6.13 ± 3.52 and 6.27 ± 2.08 , respectively. Another factor that was shown to affect severe withdrawal symptoms was previous outpatient treatments, that is, 80% of the participants who had undergone outpatient treatment before experienced severe withdrawal symptoms, whereas 46% of the participants who had never undergone outpatient treatment before had severe withdrawal symptoms. The mean anxiety score was found to be another factor having an influence on severe withdrawal symptoms. Participants who experienced severe withdrawal symptoms had higher mean anxiety scores; the average anxiety score of those without severe withdrawal symptoms was 0.68, while for those participants with severe withdrawal symptoms, it was 1.07.

Conclusions: The rate of completion of the accelerated detoxification program was very high in the study. The higher completion rate takes on particular importance considering the fact that the treatment program was only 5 days. The low rate of confusion, which is one of the major complications associated with accelerated programs, is significant insofar as it demonstrates the aptness of such programs.

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INTRODUCTION

Detoxification is a process carried out to ensure that the body can withstand the period of detoxification from addictive substances without any complications and that the withdrawal symptoms associated with the substance are mitigated and properly controlled. Withdrawal symptoms can be very damaging, especially in cases of opioid addiction. It has been shown that opioid addicts usually quit the treatment due to severe physical

and psychological withdrawal symptoms [1, 2]. In order to make it easier for the patients to complete and increase compliance with the treatment process, much effort has been put towards developing effective accelerated programs [3].

Accelerated detoxification programs, increase the completion rates of treatments by shortening the time that treatments take [4]. Rapid Opioid Detoxification (ROD)

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is defined as the administration of one or more opioid antagonists (naltrexone and / or naloxone) to patients for the purposes of accelerating opioid withdrawal and rendering the patients opioid free [5]. Therefore, such programs are also referred to as Antagonist Accelerated Withdrawal, where the aim is to administer naltrexone orally to patients or to apply a naltrexone implant subsequent to accelerated programs [6].

Naltrexone treatment, which is employed at the end of accelerated detoxification programs and is used to block the euphoric effects of opioids, is considered an alternative treatment method because it does not lead to addiction to opioid antagonists, like methadone and buprenorphine [7]. It was found in a study comparing methadone treatment with accelerated detoxification programs that patients were more likely to stay abstinent after a naltrexone treatment [8]. Krabbe et al. (2003), in their study, reported that within the first two-month period following detoxification, higher rates of patients receiving naltrexone treatment continued to stay drug free and showed less withdrawal symptoms than those of whom received methadone treatment [9]. However, the success of naltrexone treatment, in terms of increasing compliance to treatment and decreasing treatment dropouts, is still under question [10].

Accelerated detoxification programs are classified under two groups, heavy sedation/anesthesia and non - anesthetized methods. With the methods involving anesthesia, a high dose of opioid blocking substances is administered to the sedated patients. Anesthesia prevents the patient from feeling uncomfortable or from remembering the acute withdrawal symptoms. When the two methods are compared, the anesthesia method has been found to be less reliable due to its lack of a standardized method of administration and the lack of scientific data about its effectiveness. There are also concerns about the method causing life-threatening side effects [11,13].

Although there are no life-threatening adverse effects in accelerated detoxification programs that involve no anesthesia, there nonetheless may be a number of complications related to opioid deprivation and/or sedation [1]. This is why inpatient treatment is recommended in these types of programs. Intense gastrointestinal problems and cognitive impairment, such as confusion, are the most common symptoms of severe withdrawal. Other symptoms of withdrawal observed in accelerated detoxification programs include restlessness, vomiting, diarrhea, low pulse, and delirium [13,14,15].

While there have been discussions about the effectiveness of accelerated detoxification programs and the withdrawal symptoms these programs cause, studies have shown that accelerated detoxification programs hold an important place in addiction treatment because they lead to detoxification in a short time, provide 3 months of abstinence when naltrexone treatments are included, and are more cost-effective [7,16].

The possibility of severe withdrawal symptoms emerging

in accelerated detoxification programs makes the treatment challenging. However, these symptoms are not always observed in all patients [3]. From the results of studies conducted on this subject, no conclusive data has been gathered on the frequency of severe withdrawal symptoms (especially confusion and/or delirium) or on the types of patients more likely to develop such symptoms. The objective of this study, therefore, is to determine the frequency of severe withdrawal symptoms (mainly confusion) in accelerated detoxification programs and the factors determining this.

METHOD

Sample

The study was conducted with 191 patients who had been admitted to the Moodist Hospital between November 2018 and July 2019 and who were diagnosed as opioid addicts. All of the patients in the study were heroin users and underwent treatment in accordance with the Accelerated Detoxification Program (ADP) criteria set out below.

Instruments

Addiction Profile Index Clinical Form (API - CF)

The Addiction Profile Index (API) is a 37-question scale developed by Ögel et al. [17] in order to evaluate the different dimensions of addiction and to measure the severity of addiction. The scale consists of five sub-scales: substance use characteristics, addiction diagnostic criteria, effect of substance use on one's life, intense desire to use substance, and the motivation to stop using the substance. The Cronbach's alpha coefficient of the whole scale was 0.89.

The API Clinical Form (API-CF), on the other hand, was developed to specifically evaluate mental problems in clinical applications, and besides the 37 questions on the API, the API-CF includes 21 additional questions [18] addressing factors that lead to substance use, such as anger control problems, lack of assertiveness, novelty seeking behavior, impulsivity, depression and anxiety. Cronbach's alpha coefficient for this section was 0.80. Cronbach's alpha coefficient of the whole scale was 0.81 when the questions evaluating direct addiction were also included in the analysis.

Clinical Opiate Withdrawal Scale (COWS)

The Clinical Opiate Withdrawal Scale (COWS) was developed by Wesson and Ling (2003) to evaluate the severity of opiate withdrawal symptoms. Altintoprak et al. (2015) [19,20] are credited with validating the scale. To evaluate the severity of the withdrawal symptoms, the scale specifically examines subjective symptoms that emerge due to the lack of opiates, such as high pulse rate, sweating, larger pupil size, runny/watery eyes, as well as objective symptoms, like goose skin, restlessness, joint pain, gastrointestinal

issues, tremors, yawning, and anxiety/nervousness. A total score is obtained by evaluating all symptoms occurring during the withdrawal periods, and the severity of opiate withdrawal symptoms is evaluated clinically using the COWS. In this way, it is easier to follow the effectiveness of the treatment. COWS consist of 11 items that serve to evaluate both objective and subjective symptoms. It is applied and scored by the clinician. The points that can be obtained vary between 0-47, with higher scores indicating stronger withdrawal symptoms [19]. The when all factors were considered, the Cronbach's alpha coefficient was determined to be 0.83 [19].

Information about the Accelerated Detoxification Program (ADP)

Prior to admitting patients to the ADP, the patients are asked to minimize the amount of substance used before hospitalization. Information is also provided about the side effects of ADP and the problems that may occur before hospitalization before they sign the hospitalization confirmation form.

Patients who do not have good social support and who require short-term hospitalization are included in the program.

In order to decrease contraindication, patients who have any of the following are not admitted to ADP.

- Major depression
- Psychosis history
- Heart disease
- Chronic renal failure
- Severe liver disease (jaundice, encephalopathy, etc.)
- Pregnancy
- Alcohol, benzodiazepine or stimulant addiction

Naltrexone use should continue for at least 7 days due to its long methadone half-life. Patients who were on methadone were excluded from the study for purposes of securing a more homogeneous group.

During the detoxification period, Quetiapine is given for sedation, mirtazapine for insomnia, ibuprofen for pain, metoclopramide for nausea and vomiting, and loperamide for diarrhea. Fluid support is provided throughout the entire hospitalization period, including the day of discharge.

As it has been reported that pregabalin is effective in withdrawal treatment [2], it, along with benzodiazepines are also utilized in detoxification. Pregabalin is not given to patients who have pregabalin dependence.

Drug doses are adjusted according to the condition of the patient. In addition to the pharmacological treatment, group therapy and individual psychoeducation are also included.

On the 4th day of hospitalization, 25 mg of naltrexone is administered, followed by close observation for 8 hours post administration. An Additional 25 mg of naltrexone is given on the 5th day of hospitalization and close monitoring for any signs of withdrawal symptoms is performed. The

naltrexone implant is also applied on the same day.

After the implantation of the naltrexone, the patient is discharged, pharmacological treatment is planned to be reduced within one week and then discontinued and outpatient psychosocial treatment is continued for at least once a week.

Application

API-CF was applied on the first day of hospitalization, and withdrawal symptoms were evaluated every day with COWS during the hospitalization period. Incidences of confusion and/or delirium during the opioid detoxification process were considered as severe withdrawal symptoms.

Statistical analysis

Evaluations based on the API-CF could not be made for 38 patients (19.89% of the total sample), 35 of whom did not have severe withdrawal symptoms and 3 of whom did, due to patient rejection or lack of reliable information. Evaluations were conducted for only the patients who fully completed the form.

Literate patients were categorized as low, medium and high, depending on whether that had completed primary and secondary school, high school or university, respectively, in order to facilitate evaluation of their educational status. For the marital status variable, only married and single people were taken into consideration, as the data on other marital statuses were very low.

The use of cannabis, synthetic cannabinoid, cocaine, MDMA or methamphetamine once or more per month was considered as additional substance use.

The Mann Whitney U test and chi-square analysis were applied to compare the patients who quit the treatment for whatever reason with those who did not. Two-way repeated measures ANOVA (Single Factor Repeat) test was run for repeated measurements. In cases where sphericity assumption was not provided, Greenhouse-Geisser correction is applied.

RESULTS

A total of 191 patients were included in the study. The sociodemographic characteristics of the opioid addicts who were included in ADP treatment are provided in Table 1. Much of the sample consisted of males and unmarried individuals. Most of the participants resided in the same apartment or house as their families, and the rate of homeless individuals was low (Table 1). The average age of the patients participating in the study was 30.76 ±4 years.

All the participants completed the detoxification and implant insertion process. Only 1.57 % (n = 3) of the participants requested that the attachment of the implant be made on the 4th day rather than on the 5th, in order to terminate the treatment earlier.

Severe withdrawal symptoms were seen in 9.4% (n=18)

of the patients, whereas for the other patients, standard opioid withdrawal symptoms were seen. The average age of the patients with severe withdrawal symptoms was 29.16 ± 6.49 , while the average age of the patients without severe withdrawal symptoms was 29.266 ± 73 , the difference being not statistically significant (U value = 1034.50, $p = 0.99$).

The average age of starting heroin use in those with no signs of severe withdrawal symptoms was 22.08 ± 5.6 , while the average age of starting heroin use in those with symptoms of severe withdrawal was 22.13 ± 8.52 , the difference between these two groups being not statistically significant (U value = 963.5, $p > 0.05$).

The mean duration of heroin use for whole sample was 7.04 ± 5.24 . The mean duration of heroin use for those without severe withdrawal symptoms was 7.03 ± 5.16 , while for those with severe withdrawal symptoms, it was 7.13 ± 6.13 , the difference being not statistically significant (U value = 928, $p = 0.05$).

The rate of almost daily usage of opioid substances in those without severe withdrawal symptoms was 97%, while it was 100% in those with severe withdrawal symptoms ($\chi^2(4) = .45$, $p > 0.05$).

There was no difference between the distribution of the patients with and without severe withdrawal symptoms according to the type of substance they used other than opioids (Table 2). While 39.9% ($n = 55$) of those without severe withdrawal symptoms used at least one other substance once, or more than once, per month, this rate was 40% ($n = 6$) in those with severe withdrawal symptoms.

No difference was found between the groups with and without severe withdrawal symptoms in terms of whether there was an attempt to quit substance use and inpatient treatment for substance use (Table 3). The rate of outpatient treatment was higher in the group with severe withdrawal symptoms than that of the group without severe withdrawal symptoms. There was no difference between the two groups in terms of intravenous drug use, history of substitution treatment, and still being under probation status.

When the two groups were compared in terms of substance use characteristics and comorbid mental problems using the BAPI - K, the mean anxiety score was found to be higher in the group with severe withdrawal symptoms, and the difference was statistically significant (Table 4). There was no difference between the two groups in terms of addiction severity, substance use characteristics, effect of substance use on their life, cravings, and treatment motivation. The mean scores on depression, anger control difficulties, lack of assertiveness, novelty seeking behavior and impulsivity were similar between the two groups.

The COWS average scores on the first, second, third, fourth and fifth days of detoxification were found to be 6.64 ± 2.53 , 5.47 ± 2.99 , 8.14 ± 5.51 , 6.13 ± 3.52 , and 6.27 ± 2.08 , respectively, in those showing severe withdrawal symptoms, while on the same days, these scores were 5.34 ± 3.28 , 5.493 ± 22 , 5.93 ± 3.95 , 5.28 ± 3.92 , 4.82 ± 2.56 , respectively, in those not showing severe withdrawal symptoms (U value

= 495.5, $p = 0.51$). In the analysis made by repetitive ANOVA measurement with Greenhouse-Geisser correction, the change between COWS scores was not statistically significant ($F = 1.82$; $p = 0.13$).

DISCUSSION

The results from this study found that the completion rate for the accelerated detoxification program was quite high and that the rate of patients experiencing severe withdrawal symptoms, such as confusion, was 9.4%. On the first day of detoxification, severe withdrawal symptoms were higher in patients with high COWS scores, high anxiety and a higher number of outpatient treatment attempts.

The rate of completion of the program was found to be quite high. To compare, research has shown that in 3-day rapid detoxification program, the rate of completion is between 65-85% [21], yet in the present study, the completion rate was even higher than this. Considering the fact that the program applied in this study was 5 days long, its higher completion rate holds significant meaning.

The frequency of severe withdrawal symptoms in the accelerated opioid detoxification program applied in this study was found to be low. Although it is stated that withdrawal symptoms such as diarrhea, vomiting and sedation are more likely to occur in accelerated detoxification programs, there are no studies that report the frequency of the withdrawal symptoms related to these programs [7,15]. It is likely that the longer duration of the program used in this study (longer than 48 hours) influenced the low frequency of severe withdrawal symptoms. The low rate of confusion, which is one of the major complications of accelerated programs, is particularly important insofar as it demonstrates the aptness of such programs.

It was determined in the present study that high anxiety on the first day of detoxification had an effect on severe withdrawal symptoms. When the relation between anxiety and opioid dependence is examined, in addition to the comorbidity of anxiety disorders to opioid dependence, anxiety and restlessness emerge as other opioid withdrawal symptoms [22,23]. The prevalence of anxiety in opioid dependence was found to be 6% in a study conducted in China, while it was found to be 61% in a study conducted with people who were undergoing methadone maintenance treatment [24]. In a study about frequency of anxiety in opioid addiction, the comorbidity rates were found to be 56% [25].

In another study, the prevalence of anxiety was found to be 18.4% [26]. Anxiety has been reported to play a role in the early stages of recovery, and it is among the various reasons individuals quit treatment [27,28]. At the same time, anxiety has also been reported to be a factor in triggering substance craving [28]. In the present study, it was difficult to distinguish whether severe withdrawal symptoms occurred in patients with high anxiety as a comorbid mental problem, or whether severe withdrawal symptoms occurred in cases with a high number of withdrawal symptoms. Whatever the case may be, the findings clearly showed

that severe withdrawal symptoms can be observed in patients with high anxiety on the first day of detoxification. In the present study, severe withdrawal symptoms were higher in patients with high scores on the COWS scale, or in other words, in patients with high withdrawal symptoms on the first day of detoxification. While the research has shown that there may be severe withdrawal symptoms during the detoxification process, it has failed to provide information about the severity of withdrawal symptoms according to a day-by-day basis of detoxification [15]. A study comparing naloxone/buprenorphine treatments to only buprenorphine treatments shows that timing is a factor in withdrawal symptoms [29]. The findings from the present study reveal that the emergence of severe withdrawal symptoms is likely to occur subsequent to giving naltrexone on the 5th day, meaning that in order to achieve neuroadaptation to those who had severe withdrawal symptoms on the first day of the treatment, appropriate measures have to be taken.

The low number of cases with severe withdrawal symptoms in the present study was unexpected, and therefore, it is recommended that the study findings be tested for confirmation with a larger number of cases involving confusion. On the other hand, follow up studies are needed to understand the effectiveness of rapid opioid withdrawal treatment in comparison with standard treatments.

The prevalence of severe withdrawal symptoms with the detoxification program applied was not compared with the prevalence of withdrawal symptoms in standard programs. Only a limited number of studies comparing long-term opioid treatment and accelerated detoxification programs have been conducted. From those that have been conducted, it has been observed that standard programs result in less withdrawal symptoms in individuals in the early stages of treatment compared to those seen in accelerated detoxification programs; [1]. More research comparing both methods is required.

In one study, it was reported that 75% of the people followed up for 2 months subsequent to the accelerated detoxification program continued naltrexone treatment, while 25% relapsed [30]. It was further observed, in another study, that the abstinence rate was approximately 80% in treatments involving the addition of psychotherapy to naltrexone treatment and that clean results were obtained in urine tests conducted over the 6-month period following treatment [31]. Another study shows that ultra-rapid detoxification patients, in the first month 75% of the patients and in six months all the patients, relapsed [32]. It is important that comparative research on post-detoxification (remission) times in different detoxification programs be conducted.

There are only a few studies that have focused on the risks of accelerated detoxification programs and the factors affecting these risks. Against these circumstances, it is believed that this study can contribute to opioid treatment.

Table 1. Sociodemographic characteristics of the opioid addicts included in the ADP treatment

	N	%
Gender		
Female	9	5.9
Male	144	94.1
Education Status		
Low level of education	93	60.8
High level of education	60	39.2
Marital Status		
Married	44	28.9
Single	108	71.1
Economic Status		
Good	64	41.8
Medium	75	49.0
Bad	14	9.2
Living place		
In an apartment or house	151	98.7
In an institution	One	0.7
Homeless (on the street or construction site, in a shelter, etc.)	One	0.7
Household		
With family	141	92.2
Relatives, friends etc.	6	3.9
Alone	6	3.9
Job		
A regular job	95	62.1
Irregular job	14	9.2
Unemployed	44	28.8

Table 2. Distribution and statistical analyses of patients with and without severe withdrawal symptoms by type of substance they use

	Severe withdrawal symptoms				Chi Square Val.	P
	No		Yes			
	N	%	N	%		
Cannabis						
No	122	88.4	15	100	1.94	0.16
Once or more than once per month	16	11.6	0	0		
Synthetic cannabinoid						
No	106	76.8	13	86.7	0.76	0.38
Once or more than once per month	32	23.2	2	13.3		
Ecstasy						
No	131	94.9	14	93.3	0.69	0.79
Once or more than once per month	7	5.1	1	6.7		
Cocaine						
No	118	85.5	11	73.3	1.52	0.22
Once or more than once per month	20	14.5	4	26.7		
Crack cocaine						
No	91	65.9	9	60.0	0.21	0.65
Once or more than once per month	47	34.1	6	40.0		
Methamphetamine						
No	117	84.8	14	93.3	0.80	0.37
Once or more than once per month	21	15.2	1	6.7		

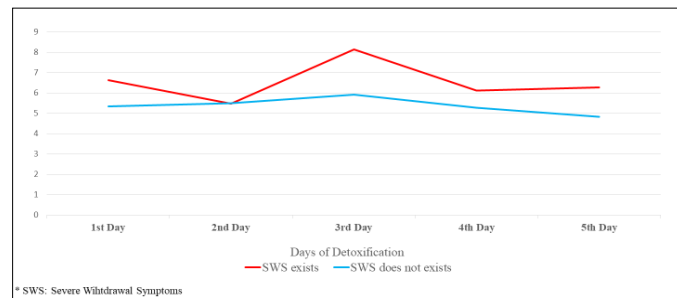
Table 3. Comparison of variables related to substance use, treatment and legal history of patients with and without severe withdrawal symptoms

	Severe withdrawal symptoms					
	No		Yes		Chi Square value	P
	N	%	N	%		
Attempted to Quit Substance Use						
Never or once	59	42.8	5	33.3	0.49	0.48
Multiple times	79	57.2	10	66.7		
Outpatient treatment						
No	74	53.6	3	20.0	6.12	0.01
Yes	64	46.4	12	80.0		
Inpatient treatment						
No	50	36.2	5	33.3	0.49	0.82
Yes	88	63.8	10	66.7		
Intravenous substance use						
No	101	73.2	12	80.0	0.33	0.57
Yes	37	26.8	3	20.0		
On Probation						
No	91	65.9	12	80.0	1.22	0.27
Yes	47	34.1	3	20.0		
Substitution treatment history						
None	37	26.8	4	26.7	0.46	0.93
Used buprenorphine	65	47.1	8	53.3		
Used methadone	8	5.8	1	6.7		
Methadone and Buprenorphine use	28	20.3	2	13.3		

Table 4. Comparison of variables with regard to substance use characteristics and comorbid mental problems in patients with and without severe withdrawal symptoms

	Severe withdrawal symptoms					
	No		Yes		U value	P
	N	Mean±SD	N	Mean±SD		
Addiction severity	138	3.050.49	15	3.190.46	888.5	0.37
Substance use characteristics	133	1.721.58	14	1.911.71	852.5	0.60
Impact on life	138	2.940.65	15	3.00.76	913.0	0.45
Craving	138	3.310.83	15	3.480.55	977.5	0.71
Motivation	138	3.90.29	15	3.960.12	1019.5	0.87
Depression	138	0.880.58	15	1.170.54	733.0	0.06
Anger	138	0.970.65	15	1.180.72	845.0	0.24
Lack of assertiveness	138	0.810.52	15	0.930.53	907.0	0.43
Novelty seeking behavior	138	0.950.64	15	0.910.72	986.0	0.76
Anxiety	138	0.680.57	15	1.070.70	701.5	0.04
Impulsivity	138	1.140.6	15	1.040.65	927.0	0.50

Graph 1. Change of severity of withdrawal symptoms according to COWS scale by detoxification day



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