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# Novel approach to predicting the likelihood of sustained abstinence in heroin addicts treated with naltrexone and naltrexone-behavioural therapy

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*Summary*

**Background:** Factors determining heroin addiction treatment outcome have not been studied extensively, despite their practical and theoretical significance. It is uncertain whether we are able to predict the odds of sustained heroin abstinence, or to influence the factors that increase the likelihood of recovery. This study has aimed to identify factors that either individually or in synergy support sustained multiannual abstinence. **Methods:** In this translational, ambidirectional cohort study, we have evaluated two groups of heroin addicts that underwent the same therapeutic procedures but with different outcomes (133 abstainers and 56 relapsers), using a non-standardized questionnaire to study: a) the history of addiction, b) motivation for the treatment, c) parental attitudes and control, d) job satisfaction, e) social and emotional relationships, f) alternative satisfactions, g) use of other substances during treatment and h) treatment characteristics. The chi square analysis was used to determine specific significant factors that act individually. Binary logistic regression provided a mathematical model of the synergistic effects of significant factors. **Results:** The study found a new variable, an 'abstinence marker', which was defined by the synergistic effect of the following factors: a) use of tramadol before treatment ($p = 0.011$), b) non-use of benzodiazepines ($p = 0.001$), c) length of naltrexone use ($p < 0.0005$), d) non-use of cannabis ($p = 0.002$), e) non-compulsive exercise ($p = 0.009$), and f) employment and job satisfaction ($p < 0.0005$) during recovery. **Conclusions:** This study reports a mathematical model that predicts multiannual sustained abstinence as an outcome of heroin addiction treatment.

*Key Words:* Heroin addiction; treatment outcome; naltrexone; abstinence

## 1. Introduction

Heroin addiction is a chronic, progressive and recurrent disease. The optimal treatment outcome of total abstinence from opiates is seldom achieved [47, 16, 11]. Some studies have provided evidence that it is possible to sustain multiannual abstinence from opiates and opioids as an outcome of heroin addiction treatment [32, 23, 28]. Achieving recovery is a lengthy process whose dynamics and determing factors we still do not understand fully [23, 28].

The use of μ- opioid receptor antagonist naltrexone (NTX) can help achieve long-lasting abstinence from opiates [44, 49, 24, 25]. The positive sides of NTX in sustaining stable abstinence in heroin addicts include lack of abuse potential and the ability to act as a strong anti-craving medication, not only for opiates, but also for alcohol and other substances [40, 49, 50, 15, 18, 19, 5]. Furthermore, there is evidence that the use of NTX significantly reduces the possibility of death from heroin overdosing [22]. One of naltrexone's drawbacks is that it does not promote self–administration, due to the lack of any agonistic effect. Retention in treatment and compliance are of great importance in determining the outcome of therapy [35, 30, 47, 31, 23, 28]. Combining NTX with a psychosocial treatment increases the chances of overcoming non-compliance [40, 49]. More specifi-

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cally, in naltrexone-behavioural therapy (BNT), NTX is used in combination with evidence–based treatments, including motivational interviewing, cognitive behavioural relapse prevention, voucher incentives and network therapy. BNT may contribute to the patient's genuine motivation for treatment [4, 5, 27, 11, 38, 49].

### *1.1. Impact of use of other psychiatric medications and substances on heroin addiction treatment*

Heroin addicts often substitute heroin with available opiates and non-medically used prescription opioids for practical or psychological reasons [17, 51]. Examples of these substitutes include tramadol (TRM), 'poppy cocoon tea', methadone, buprenorphine, codeine and morphine. To better understand their impact on addiction treatment, we need to elucidate the significance of a substitute choice. The antidepressive, anxiolytic and antipsychotic properties of opiates as a pharmacological category have been widely recognized by the scientific community. More specifically, it does seem that TRM is able to provide a strongly antidepressant effect, compared with other opioids, since it also suppresses the reuptake of serotonin and norepinephrine. In addition, the anti-depressant effects of TRM have been shown in animal models of depression and in several preclinical studies, so leading to it being increasingly considered as a suitable therapy for depression treatment [52, 55].

The impact of using other substances during recovery from heroin addiction on the treatment outcome has been explored in many studies. Those studies suggest the negative impact of related substance abuse on the clinical presentation of heroin addicts. In particular, cocaine abuse has shown to increase the likelihood of psychiatric disorders and to lower the subject's awareness of his/her own psychopathology [6]. Similarly, it has been shown that heroin addicts may mask heroin use with alcohol abuse, so continuing addiction patterns that may be disguised as remission [39]. Among those other substances, cannabis has been studied the most extensively, as its abuse is frequent among opiate addicts even during their recovery [40, 14]. Clinicians are often faced by the dilemma of whether to insist on abstinence from all substances during the treatment of opiate addicts, or to tolerate the use of substances such as nicotine and cannabis [33]. Several studies have shown that the use of cannabis impedes heroin addiction treatment or produces worse outcomes [54, 1], and results in a 27% reduction in the odds of abstinence from drug and heavy alcohol use [33]. In contrast, other studies, e.g. Saxon et al. [42], showed that patients using cannabis were less likely to use other psychoactive substances. Additionally, in some studies, e.g. Epstein and Preston [14], the use of cannabis did not have an impact on the duration or outcome of heroin addiction treatment [10, 12, 14]. Other studies have suggested that the use of cannabis may increase the odds of a patient staying in treatment and sustaining abstinence [40, 42]. It has also been reported that cannabis use correlates positively with retention in treatment and taking naltrexone [40, 12]. Studies by Wasserman et al. and Aharonovich [1, 54] indicated the worse outcome of treatment of opiate addicts who had been abusing cannabis.

Interactions between cannabinoid and opioid systems are being focused on by research goups. The study of Haney M. et al. shows that naltrexone maintenance decreases self-administration and the subjective effects of cannabis [19].

Although some studies found no correlation between the heavy use of benzodiazepine (BZ) and either treatment abandonment or successful abstinence [8], Stella et al. showed that the use of prazepam in the early abstinence of patients treated with NTX reduced symptoms such as dysphoria, while increasing the odds of sustaining abstinence [48]. Similarly, in the study of Hubbard and Marsden the largest number of relapses was found in the group of addicts that used heroin alone [21]. Given these contradictory reports, the present study includes variables related to the abuse and misuse of substances other than heroin before the treatment and during heroin addiction treatment and recovery.

### *1.2. Impact of behavioural and environmental factors on heroin addiction treatment*

A famous study by Alexander et al. [3] named "Rat Park" showed the significance of environmentsl factors, suggesting that the use of heroin is a choice that a "happy rat" would not make [3]. This revolutionary study showed that rats found in an inspiring environment that offers different types of comfort, would not choose heroin, unlike rats that found themselves in an uninspiring environment [2]. Although clinical experience suggests that employment itself and satisfaction with one's job are significant factors in developing healthy lifestyle habits during recovery, there are too few studies on the correlation between employment and successful long-term abstinence. Silverman et al. found that employment is a signifi-

cant factor in sustaining the abstinence of cocaine addicts and that a job serves as an additional protective agent [46]. Furthermore, De Fulio et al. confirmed that an adequate monetary compensation, if coupled with the employer's request for abstinence, increases an addict's chance of sustaining abstinence [13].

Physical activity may be regarded as a behavioural factor that significantly improves the quality of life and chances of recovery from heroin addiction [20] and there are an increasing number of studies on the neurobiological basis of this phenomenon. Meta-analysis of 22 randomized control trials conducted from 1990 to 2013 showed that physical activity might increase the abstinence rate, significantly more so in the case of illegal drug addicts than in the case of alcohol and nicotine addicts [53]. The study found that moderate and intense aerobic exercise, and mind-body exercise both contribute to a positive addiction treatment outcome. Possible mechanisms by which physical activity affects the possibility of a relapse include its effect on glutamatergic and dopaminergic signalling and chromatin remodelling in reward pathways [26]. In addition, exercise seems to have a significant effect on specific molecular systems regulating neuroplasticity [7, 37, 38]. Specifically, sustained cardio training leads to a long-lasting increase in the level of Brain Derived Neurotrophic Factor (BDNF) in the hippocampus of experimental animals. This leads to adult hippocampal neurogenesis and synaptogenesis, and the enhancement of learning and memory [37, 38]. Higher production of BDNF in the hippocampus exerts a long-lasting therapeutic effect by removing the damage done to nerve cells by continuous substance abuse [37, 7, 26, 53].

Though beneficial in reducing craving and risk for relapse, exercise might have no effect or even lead to harmful effects, depending on the intensity, frequency, type and especially timing of practice during the treatment of heroin addiction [26]. Exercise, if initiated at a late stage during abstinence may mimic the effect of substance use. It may lead to further increases in dopaminergic and glutamatergic signalling, causing the enhancement rather than the attenuation of drug seeking. Forced exercise, particularly at high intensity levels, may actually enhance drug seeking in response to drug use [26].

In this study we hypothesize that it is possible to develop the mathematical model to investigate the relationship that significant factors have to sustained abstinence. This formula can then be used to predict the success of the treatment, manipulate given factors to optimize therapeutic interventions and raise the likelihood of achieving the desired treatment outcome.

## 2. Methods

### *2.1. Sample*

This ambidirectional cohort study used a stable patient population of 189 heroin addicts treated in the Lorijen Hospital clinic for at least 24 months. The experimental group consisted of 133 heroin addicts with uninterrupted, continuous abstinence from heroin and all other opiates and opioids lasting from 24 to 126 months. It should be noted that at the time of the study, nearly half of the participants (45%) had been abstinent for 3 to 10.5 years. The control group consisted of 56 relapsers who had been treated for more than 24 months, but who failed to stabilize abstinence and sustain it for more than 6 months. Participants were mostly men (159 men and 30 women), aged 25 to 40. The two groups were equal in terms of sociodemographic data and addiction history.

### *2.2. Instruments*

On the basis of our clinical experience and relevant data from the professional literature, we developed the questionnaire consisting of 136 questions and three types of variables: interval, binary and categorical, divided into the following thematic areas: a) sociodemographic variables, b) addiction history, c) motivation for treatment, d) parental attitude and control during treatment, e) employment and job satisfaction, f) social and emotional relations, g) alternative satisfactions, h) NTX use, i) type and duration of psychotherapy, j) abuse and dependence on other substances, and behavioural addictions, and k) marriage and parenthood after the treatment began. All respondents filled in the questionnaire following the same instructions and under the supervision of the clinical psychologist.

All participants underwent the same diagnostic procedures: 1) psychiatric and physical assessment, 2) standard laboratory analyses, and 3) standard therapy procedures including: a) hospital detoxification and amelioration of the opiate withdrawal syndrome using clonidine, lorazepam and other symptomatic medications, b) induction of NTX (first day 25 mg, second day 50 mg) and continuing NTX therapy under the supervision of a significant other, and c) individual psychotherapy treatment (BNT) two times per week. Experimental variables were duration of NTX

use and time spent in the psychotherapeutic setting. Abstinence control was performed clinically, at a frequency suitable for the treatment stage. The treatment programme envisaged regular checks on opiate and opioid use through urine screening in the clinic – twice a week during the first three months (corresponding to the frequency of psychotherapy sessions), and once a week during the next three months. From the sixth to the twelfth month, urine screening was performed once every two weeks, during each check-up. During the second and third year, it was performed once a month, each time a patient came for a check-up and naltrexone prescription. Afterwards, it was performed once every three months. Significant others (companions in treatment) were instructed to perform home screening in any case when there was a doubt based on the appearance and behaviour of the patient. After the first year of abstinence, when the visits to the clinic became less frequent, they were invited to perform home screening regularly once every two weeks. Abstinence was also assessed when selecting patients for the study, through a psychiatric evaluation, inspection of the patient's medical records, auto- and heteroanamnestic data (from significant others) and control screening of urine for opiates and opioids.

### *2.3. Data analysis*

We applied descriptive statistical measures: arithmetic mean, standard deviation, median, quartiles, frequencies and percentages. The Mann-Whitney test was used to compare the mean values of variables for the two populations. The correlation between categorical variables was assessed using the chi square test for contingency tables. The impact of assessed variables on abstinence was determined by using univariate and multivariate binary logistic regression. We used ROC curves to assess whether a variable may indicate abstinence, after determining the optimal value, sensitivity and specificity of each variable. Data were processed in the SPSS programme.

## 3. Results

Binary logistic regression confirmed our hypothesis that there are factors that influence one's ability to sustain abstinence from heroin. This same method was used to develop the mathematical model of synergy between significant factors that, taken together, make up what we have named our 'abstinence marker'. In accordance with the aim of the research, we determined a variety of protective factors and their percentage occurrence.

Male sex was predominant both in the group of abstainers (82.7%) and in the group of relapsers (87.5%). The mean age of the abstainers was 32.4 ± 4.69 years, and of the relapsers was 31.20 ± 4.89 years. The average length of education of abstainers was 12.87 ± 2.13, and of relapsers was 12.27 ± 2.03 years. The average age at which participants started experimenting with psychoactive substances was 17 years and with opiates 19.6 years for both groups.

The findings of this study indicate that the factors showing a significant relationship with the treatment outcome included: a) the use of other psychoactive substances (TRM, BZ and cannabis), before, during and after treatment, b) therapy factors (use of NTX and duration of psychotherapy treatment), and c) behavioural factors such as sports, employment and job satisfaction. The chi square test showed a correlation between the treatment outcome and the factors studied.

As seen in Table 1, multivariate binary logistic regression identified the cluster of factors that, when acting in synergy, contribute to multiyear abstinence as an outcome of heroin addiction treatment. Abstinence is largely determined by the use of TRM before treatment ($p = 0.011$), non-use of a BZ during recovery ($p = 0.001$), prolonged use of NTX ($p < 0.0005$), non-use of cannabis in large doses ($p = 0.002$), not exercising compulsively ($p = 0.009$) and job satisfaction ($p < 0.0005$).

Furthermore, we found that a participant taking TRM with heroin prior to treatment had a nearly 4 times better chance of sustaining abstinence (odds ratio for TRM use was 3.858 [range 1.367-10.890]). In contrast, taking benzodiazepines was found to decrease fivefold the chance of sustained abstinence (odds ratio 0.183 [0.066-0.510]). Participants with frequent cannabis use proved to have around 2 times less chance of sustaining abstinence (odds ratio 0.530 [0.353-0.794]). NTX use was identified as a significant factor, with each new month of NTX use increasing the chance of sustaining abstinence by around 13.7% (odds ratio 1.137 [1.076-1.202]). So too categories of job satisfaction (highly unsatisfied, unsatisfied, partially satisfied, and satisfied) had a significant impact on the outcome, with each successive listed category that implies an improvement in job satisfaction improving the odds for sustaining abstinence by around 62% (odds ratio 1.619 [1.240-2.113]).

The chi square test confirmed the inverse cor-

**Table 1.** Factors predicting sustained heroin abstinence

| | Univariate binary regression | | Multivariate binary regression | |
|---|---|---|---|---|
| Variable | Odds ratio | p | Odds ratio | p |
| Use of TRM before treatment | 2.947 (1.490-5.830) | 0.002 | 3.858 (1.367-10.890) | 0.011 |
| BZ during recovery | 0.426 (0.316-0.574) | < 0.0005 | 0.183 (0.066-0.510) | 0,001 |
| Months of NTX taking | 1.123 (1.072-1.177) | < 0.0005 | 1.137 (1.076-1.202) | < 0.0005 |
| Cannabis during recovery | 0.585 (0.450-0.761) | < 0.0005 | 0.530 (0.353-0.794) | 0.002 |
| Exercise during recovery | 0.326 (0.142-0.748) | 0.008 | 0.228 (0.075 -0.693) | 0.009 |
| Clearly set goals | 3.400 (1.525-7.580) | 0.003 | | |
| Job satisfaction during recovery | 1.487 (1.242-1.781) | < 0.0005 | 1.619 (1.240-2.113) | < 0.0005 |
| Cocaine during recovery | 0.535 (0.382 – 0.748) | < 0.0005 | | |
| Loss of behavioural control as a motivation for treatment | 0.485 (0.257-0.917) | 0.026 | | |
| Socialization during heroin abuse | 1.604 (1.318-1.953) | < 0.0005 | | |
| Type of psychotherapy | 1.153 (1.004-1.325) | 0.044 | | |
| Duration of psychotherapy | 1.591 (1.259-2.010) | < 0.0005 | | |
| Gambling during recovery | 5.773 (2.044-16.303) | 0.001 | | |
| Parenthood during recovery | 1.452 (1.071-1.969) | 0.016 | | |
| Unemployment during recovery | 0.277 (0.144-0.533) | < 0.0005 | | |
| Clear goals, unreached | 3.497 (1.814-6.739) | < 0.0005 | | |
| Antidepressants during recovery | 0.478 (0.250-0.915) | 0.026 | | |

relation between the use of TRM if taken in parallel with heroin before treatment and abstinence (p = 0.003). More specifically, 17.9% of patients taking TRM side by side with heroin relapsed, compared with 39% of patients who did not take TRM, so demonstrating that addicts using TRM have significantly higher chances of achieving sustained abstinence once they start the treatment. As expected, the chi square test showed that addicts who use BZ during treatment have a statistically lower chance of achieving sustained abstinence (Table 2).

Our results indicate that there is a complex relationship between cannabis use and sustaining abstinence. More specifically, a significantly higher percentage of patients not taking cannabis were abstainers (87.3%) than relapsers (12.7%). This difference in outcome was still demonstrable in groups whose use was rare or occasional (62% vs 38%), whereas the chances of achieving abstinence diminished with frequent or daily use of cannabis (Table 3). It was shown that frequent cannabis use significantly (p < 0.0005) reduced the chances of sustaining abstinence and of becoming abstinent by approximately 50% (Odds ratio was 0.530 [0.353-0.794]).

As shown in Tables 1 and 4, NTX use and the duration of its use significantly affect the treatment outcome and success in sustaining abstinence (odds ratio was 1.137 [1.07- 1.202]). There were 72.8% and 43.8% of abstainers in the two groups of patients – the first using and the second not using NTX (Table 4). The difference in the mean value of the length of NTX use between abstainers and relapsers was statistically significant (p <0.0005). Abstainers used NTX for 16.13 ± 7.85 and relapsers for 6.22 ± 12.77 months on average. Moreover, the results showed that a patient's sex is not correlated with NTX use (p = 0.080), as 89.9% of male and 100% of female participants used NTX. Importantly, the duration of NTX use was identified as one of the abstinence markers (area = 0.776, p <0.0005, sensitivity of 71.0% and specifi-

**Table 2.** Use of benzodiazepine among abstainers and relapsers

| | Abstainers | Relapsers | p |
|---|---|---|---|
| Did not use BZ | 63 (88,7%) | 8 (11.3%) | < 0.0005 |
| Used BZ | 70 (59,3%) | 48 (40.7%) | |

**Table 3.** Cannabis use among abstainers and relapsers

| | Abstainers | Relapsers | p |
|---|---|---|---|
| No use of cannabis | 69 (87.3%) | 10 (12.7%) | 0.015 |
| Rare use of cannabis | 24 (61.5%) | 15 (38.5%) | |
| Occasional use of cannabis | 23 (62.2%) | 14 (37.8%) | |
| Frequent use of cannabis | 10 (47.6%) | 11 (52.4%) | |
| Daily use of cannabis | 5 (50.0%) | 5 (50.0%) | |

**Table 4.** Naltrexone use among abstainers and relapsers

| | Abstainers | Relapsers | p |
|---|---|---|---|
| Did not use NTX | 7 (43.8%) | 9 (56.3%) | 0.015 |
| Used NTX | 126 (72.8%) | 47 (27.27%) | |

city of 73.2%). Cut-off was identified at 7.5 months, indicating that NTX should be used for at least that long to achieve the maximum therapeutic benefit. It was also found that each new month of NTX use increased the chance of a successful outcome by 13.7%.

It is presumed that the absence of exercise, employment and, especially, job satisfaction has a strong impact on abstinence. According to our results absence of exercise ($p = 0.009$) and job satisfaction ($p < 0.0005$) both contribute significantly to sustaining abstinence. Job satisfaction, along with the duration of NTX treatment, was found to be one of the most important factors that allow sustained abstinence to be achieved (Table 1).

Using binary logistic regression we identified coefficients that express the contribution of each significant factor on the treatment outcome (Table 5). These coefficients were applied in the following formula to define the new variable called by us the 'abstinence marker':

$$\text{the abstinence marker} = \exp(\text{sum})/(1+\exp(\text{sum}))\cdot 100, \text{ whereby}$$
$$\text{sum} = 3.267 + 1.350 \cdot a - 1.689 \cdot b + 0.129 \cdot c - 0.636 \cdot d - 1.477 \cdot e + 0.482 \cdot f.$$

Our ability to fully identify an applicable abstinence marker confirms the existence of a specific set of factors that, taken together, may be considered a predictor of sustained abstinence. The values for this marker range from 0 to 100. This variable is a robust marker of abstinence (area = 0.838, $p < 0.0005$). The optimal cut-off for predicting abstinence is 74, with a sensitivity of 86.8%, and a specificity of 85.5%. The difference in the mean value of the new variable between abstainers and relapsers is statistically significant ($p < 0.0005$). In our study the mean value of the abstinence marker in relapsers was 30.66 (range 11.94-48.03), and in abstainers it was 93.83 (range 82.74-98.45).

The value of the abstinence marker was significantly correlated with abstinence ($p < 0.0005$) (odds ratio was 1.062 [range 1.046-1.079]) and the increase in the value of this variable by 1 was found to increase the chances of abstinence by 6.2%. The Hosmer–Lemesh test shows that the variable abstinence marker shows a good fit with abstinence (i.e., it is effective in predicting the chances of a patient becoming abstinent). By applying the values of the abstinence marker to our patient population, we were able to confirm an excellent correlation. For example, the calculated value of this marker for a patient in our study who was abstinent is 99.75, implying that the chance of him/her being abstinent is as high as 99.75%. In contrast, the value of this marker in a patient who was not abstinent was 4.16, indicating a chance of achieving abstinence as low as 4.16%.

## 4. Discussion

This study identified significant factors affecting heroin addiction treatment outcome and constructed a mathematical model for the synergistic effect of these factors, with the aim of selecting a reliable abstinence marker. Individual factors that proved to be significant in sustaining abstinence include the use of TRM as a heroin substitute before treatment, non-use of BZ during treatment, absence of the extensive use of cannabis, longer use of NTX, physical activity and job

**Table 5.** Factors significantly affecting heroin addiction treatment outcome

| Variable | Symbol | Coefficient |
|---|---|---|
| Use of TRM before treatment | a | 1.350 |
| Use of BZ during recovery | b | -1.698 |
| Months of NTX use | c | 0.129 |
| Use of cannabis during recovery | d | -0.636 |
| Exercise during recovery | e | -1.477 |
| Job satisfaction during recovery | f | 0.428 |
| Constant | | 3.267 |

satisfaction.

This study shows that TRM use before treatment tends to compensate for the lack of heroin or, in cases of self-medication, increases fourfold the chance of a heroin addict achieving sustained abstinence for longer than two years, while the alternative in the form of other opiates and opioids instead of heroin (e.g., methadone, poppy cocoon tea) before the start of treatment did not act as a protective abstinence factor. TRM is a synthetic opioid with weak agonistic effects on μ-opioid receptors. Owing to its opioid effect, TRM has antidepressive, anxiolytic and antipsychotic properties. TRM also suppresses the reuptake of serotonin and norepinephrine, thus causing an antidepressant effect similar to that of venlafaxine [52, 55]. Clinical experience shows that TRM is 'a drug of choice' for depressed and socially anxious people. It may also be presupposed that previous experience with TRM – a factor that alleviates both the withdrawal syndrome and the accompanying emotional disturbances (such as depression and social anxiety) – served as an encouragement for the new treatment and induced more optimism in heroin addicts about the success of their recovery. Due to the weak agonistic effect on μ-opioid receptors, TRM suppressed the craving and compulsion of heroin addicts, while the antidepressant effect encouraged their determination to seek better solutions, as well as healthier and more efficient ways to combat addiction [23, 29].

The study showed that BZ abuse leads to a fivefold reduction in the chance of sustaining opiate abstinence for longer than two years. This contradicts the study by Stella and co-workers [48] according to whom the medical use of prazepam during the early abstinence of patients treated with NTX helped reduce dysphoria and other symptoms, while raising the chances of sustaining abstinence. It also contradicts the results of the study by Hubbard and Marsden [21], which found that the largest number of relapses were those among addicts who used heroin alone. The reason for discrepant results between these two studies may lie in the fact that the first study evaluated the effect on early abstinence. The long-term use of a partially cross-tolerant drug such as benzodiazepines might reflect an unbalanced opioid debt and post-withdrawal symptomatology not alleviated by naltrexone. The possible explanation for the negative effect of prolonged BZ use on achieving sustained abstinence may be related to a BZ-induced fall in cognitive activity, the acquisition of new knowledge, and ongoing psychological development. We may presuppose that a negative correlation with achieving sustained abstinence through the intensive use of cannabis is due to effects identical to those seen with BZ.

Results of our study partly confirmed the findings of recent studies that the moderate use of cannabis increases the likelihood of sustained abstinence [40, 42, 43, 10, 12, 14]. On the other hand, another of our findings was that frequent cannabis use during treatment halves the chance of sustaining abstinence longer than two years, which is in line with findings by Mojarrad and co-workers [33], Wasserman and co-workers [54] and Aharonovich and co-workers [1]. Unlike these previous studies, we stratified our patients according to the intensity of marijuana use, and this lack of differentiation might be the reason for the apparent discrepancy between various studies.

Opiate withdrawal syndrome (WS) is a result of hyperactivity in locus coeruleus (LC). By inhibiting LC, cannabinoids reduce the hyperactivity of the sympathetic nervous system in opiate WS [43], so it is possible that moderate cannabis use in early abstinence helps reduce subacute WS, but also hyperexcitability and insomnia related to NTX use. In the latter course of treatment, the more substantial risks related to cannabis abuse include amotivational syndrome and contacts with dealers, which lower the chance of qualitative changes during the treatment. Specifically, learning new coping skills and developing mature intrapsychic patterns require adequate and persistent

motivation and intact cognitive abilities.

Clinical and animal studies indicate numerous interactions between the opioid and endocannabinoid systems. Activating cannabinoid CB1 receptors facilitates the restorative effect of opioids. This may underlie the synergistic effects of the prolonged use of NTX and a reduction in cannabis use [19]. This finding has significant implications when choosing a pharmacotherapeutic protocol for the treatment of opiate addiction. All CNS depressants become opiate substitutes, which is helpful in early abstinence but with time helps maintain the addiction pattern by preventing more adaptive changes in behaviour.

In accordance with other studies, we found that the duration of NTX use, combined with other protective factors, significantly affected the stabilization and sustaining of abstinence [46, 50, 25, 26]. Each new month of NTX use increased the probability of abstinence by 16.7%. We believe that this NTX effect is mediated not only by its suppressive effect on opiates implemented through the pharmacological blockage of receptors, but also by NTX's anti-craving effects [51, 15, 5, 18]. The issue of compliance in NTX treatment is best addressed through therapeutic support, inclusion, and education of the patient's partner, so that she/he could become a constructive companion during treatment.

Contrary to our own expectations, and the findings of other studies [26, 37, 52], the results of the present study indicate that certain types of physical activity reduce the likelihood of sustained abstinence. While moderate physical activity during early abstinence helps with time management, improves mood, lowers anxiety and improves long-term cognitive abilities, it seems that excessive and compulsive exercise, when introduced at a late stage in abstinence, reactivates cognitive, emotional and behavioural addiction patterns [26]. Furthermore, according to Shaffer and addiction syndrome theory, most addicts are prone to substitute one addiction with another [45], for example heroin with 'exercise addiction', so that a true WS develops in cases of exercise deprivation. Our results indicate that the substitution of heroin not only with other addictive substances (BZ, cannabis), but also with addictive activities (compulsive exercise, gambling), reduces the likelihood of sustained abstinence. Additional studies with a specific focus on exercise during heroin addiction treatment are needed to distinguish conditions that would support the beneficial from the harmful effects of exercise.

Our study has confirmed the importance of job satisfaction as another behavioural factor that has a positive impact on the outcome of heroin addiction treatment [13].

The synergistic effect of factors such as BZ and cannabis that have a negative impact on recovery from addiction can be explained by their shared ability to weaken the will, psychic tone and cognitive abilities during treatment, while these convergent forms of impediment disrupt the learning process. The concomitant use of BZ and cannabis has an additional anxiolytic effect through the interaction of the cannabinoidergic and the GABAergic systems [34]. Use of NTX over a sufficiently long period can be the factor that connects this cluster through its effect on cannabis use [19].

## 5. Conclusions

The conclusion will give prominence to the factors that are likely to have a significant impact on the chances of achieving sustained abstinence. The synergistic effect of these factors is of particular importance, and can be expressed in a mathematical model.

The findings reported in this study have important implications for addiction treatment. What is vital to treatment success is being able to keep NTX, provided it is used in sustaining abstinence, as long as possible in the treatment, to cover a period of at least 7.5 months. Substances that maintain cognitive decline, such as BZ, and regular cannabis use to the extent that it impedes everyday life and mental activity, should be avoided. The psychotherapeutic setting should support gaining new experiences, psychological awakening, and cognitive activity, while encouraging emotional content that leads to activation of the overall psychological apparatus, as opposed to inner numbness. Regular sports activities should be incorporated early into addiction treatment plans, but more studies are needed to elucidate their effects on the later stages of abstinence. An excercise plan should be monitored closely in order to avoid the substitution of activities that have beneficial effects on recovery with an excessive and compulsive physical activity.

Finally, patients undergoing heroin addiction treatment should be encouraged to seek a job if possible, as it brings not only a new structure of time, but also a sense of achievement and inner satisfaction.

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All authors declare no conflict of interest.

*Ethics*

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

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